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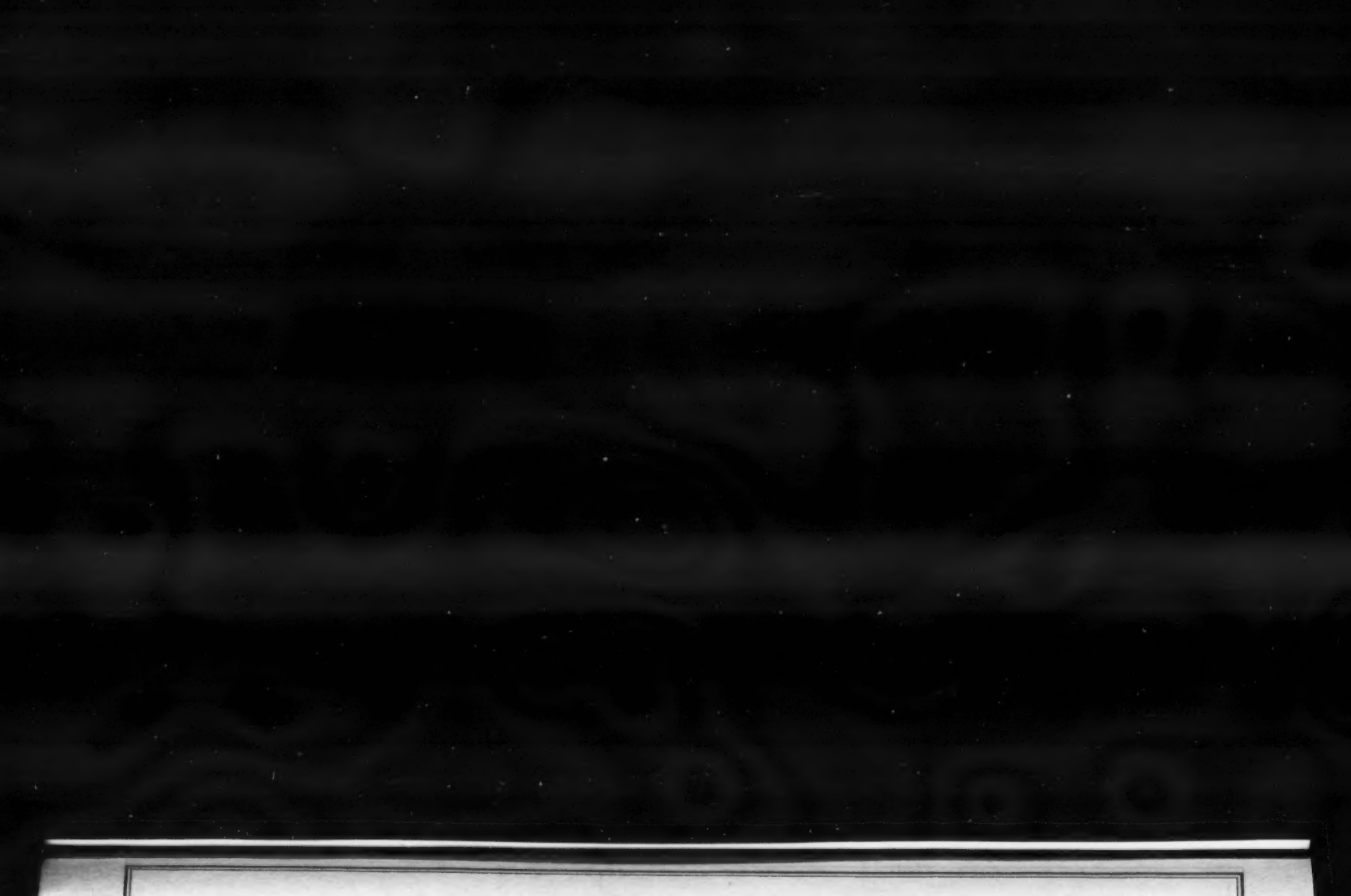

THE PROGNOSIS OF ACUTE GLOMERULAR NEPHRITIS IN CHILDHOOD

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During the past twenty years nephritis in children as a problem in itself, apart from nephritis in adults, has attracted considerable attention. At first, thought was directed mainly toward etiology and classification and gradually a uniformity of opinion on these two phases of the problem, sufficient for practical purposes, has been reached. Of recent years interest has turned more toward prognosis. Now that the rôle of infection as an etiological factor is appreciated, and a clinical classification[1] into (1) glomerular or hemorrhagic nephritis, (2) tubular nephritis or nephrosis, and (3) the mixed forms, is generally recognized, it is possible to investigate this third phase of the problem in a systematic way.

The object of this paper is to present a study of the prognosis in acute hemorrhagic or glomerular nephritis in children as determined by follow-up examination of patients seen in the Harriet Lane Home from 1912 to 1928 suffering from this disease. The diagnosis in these cases was based on the accepted criteria for this form of nephritis, namely, a fairly acute onset of symptoms, usually following an acute infection, the presence of varying amounts of edema, associated in a large proportion of the cases with elevation of blood pressure, and the appearance in the urine of albumin, casts, and red blood cells. As the cases of tubular nephritis or nephrosis that have been observed in the Harriet Lane Home have been reported previously by Davison and Salinger (1), no attempt has been made to investigate these. There were, however, cases of nephritis in the Harriet Lane Home files not included in this study which may possibly have belonged in it.

[1] This classification is not intended to convey the impression that pathologically in (1) the lesions are solely glomerular and in (2) solely tubular—only that one or the other lesion predominates in relation to a given clinical picture, while in the mixed forms the outstanding characteristics of both are combined.

They concerned children who appeared at the time of admission to have passed, without clearing of signs or symptoms, from an illness of indefinite onset several months before they were seen here into a subacute or chronic one with the characteristics of a combination of glomerular and tubular nephritis. As it was not possible to determine from the histories given that the picture at onset was that of a glomerular nephritis, it seemed best to classify these in the mixed group. All those patients have been included, however, in whom the diagnosis of acute glomerular nephritis was unquestionable from the very beginning of symptoms throughout the period of observation in the hospital, according to the criteria mentioned.

One of the first and probably the best known study of the prognosis in acute nephritis in children is that of Ernberg (2). In 1911 Ernberg reported the results of examinations of forty adults who had had acute nephritis before the age of fifteen, and of sixteen who had had it between the ages of fifteen and thirty. In four of the latter the urine showed some abnormality, but in all of the forty who had had nephritis in childhood, at an age corresponding to that of our patients, the urine was entirely normal.

During the next few years many papers were written on nephritis in children from the standpoint of etiology, classification and symptomatology, but they gave little more than general impressions without actual statistical studies in regard to prognosis. An extensive review of this literature was made by Hill (3), in 1917, in preparation for his statistical study of nephritis, published in 1919. In that year (1919) (4), with attention directed particularly toward prognosis, Hill reported on 75 cases of nephritis admitted to the Children's Hospital in Boston during the preceding two and one-half years. The diagnosis of acute glomerular nephritis was made in 49 cases. In 8 of these the illness was extremely severe, but in only one did death occur. In 41 cases (84 per cent) complete recovery took place, after an illness that averaged seven to eight weeks in duration, although in several a trace of albumin persisted in the urine for four or five months. Hill concluded that the majority of children with acute glomerular nephritis, who recover, recover completely and their kidneys are not more susceptible to damage than are those of children who have never had nephritis.

In 1921, James (5) again reviewed the literature and reported a study of 70 children, who had been seen in the Children's Hospital in Boston with nephritis during the preceding sixteen years. This study of James, no doubt, included some of the cases reported by Hill, as the interval since the attack of nephritis varied from three months to sixteen years. Of the 70 cases examined by James, 67 of the children had been admitted with acute glomerular nephritis. All of these were symptomatically well at the time of the follow-up examination and were living under ordinary conditions on a general diet. Nine of the sixty-seven were regarded as having developed a chronic nephritis because of a persistent trace of albumin in the urine or some fixation of specific gravity or slight elevation of blood pressure. The other 58 patients (86 per cent) were found to be entirely normal in all respects. One of the patients in the group in which the nephritis was thought to have become chronic had had several recurrences of his nephritis with upper respiratory infections, yet five of the group in which complete recovery appeared to have occurred had passed through rather severe acute infections without recurrences.

Osman (6), in 1925, reported in *Guy's Hospital Reports* a study of 56 cases of nephritis examined 18 months to 22 years after the onset. The examination did not include renal function tests but consisted solely in clinical and urinary examinations. Thirty-six patients were found to be entirely normal and twenty were believed to show some evidence of renal impairment. In five of these latter cases, however, the urine was entirely normal and a slightly elevated blood pressure was the only abnormality found. Osman tabulated his cases. He concluded that there is "no relation between the severity of the original illness, the treatment and the outcome."

In 1926 Clausen (7) analyzed 129 cases of nephritis at Marriott's Clinic in Saint Louis. His paper deals more with a discussion of the comparative etiology, symptomatology and laboratory characteristics of glomerular and tubular nephritis than with prognosis. He gives, however, as figures for the outcome in 102 cases of glomerular nephritis, 73 complete recoveries (71 per cent), 20 deaths (pneumonia, pertussis and sepsis among the causes of death, which was, therefore, not in every case attributable to the nephritis itself) and 9 terminations in a chronic disease of the kidney. No data are given to show how serious were the evidences of the chronic nephritis.

In a discussion of Parsons' paper on acute nephritis in children (8), presented in 1926, Smellie states that on examination of 16 of 47 patients seen ten years after their nephritis he found 10 who were well according to life insurance requirements, and 6 with slight cardiac enlargement and elevation of blood pressure, which could not be attributed to the previous nephritis since the urine was entirely normal.

Also, in 1926, Paterson and Wyllie (9) reported the results of examination of 49 children who had had some form of acute nephritis three and a half to five and a half years previously at the Hospital for Sick Children, Great Ormond St., London. It is somewhat difficult to compare the results of Paterson and Wyllie with ours as they used a different classification. Under the heading of parenchymatous nephritis they included both tubular nephritis and those cases of glomerular nephritis in which edema was one of the outstanding symptoms, while those cases of glomerular nephritis in which there was marked hematuria without much, if any, edema they grouped separately under the heading of hemorrhagic nephritis. Of 22 cases in the "parenchymatous" group, six children had died, five had made a complete recovery, six though in good health showed abnormal urinary constituents, and five showed "obvious signs of chronic nephritis." Of 27 cases in the "hemorrhagic" group, one had died of tuberculous meningitis, twelve had made a complete recovery and nine showed abnormal urinary constituents, although otherwise in good health. Of the remaining five, one had recurrent hematuria, three, besides showing abnormal urinary constituents, appeared "unhealthy," and one had a real chronic nephritis with evidence of renal impairment. Their statistics are, therefore, somewhat more gloomy than the others, since even in the hemorrhagic group less than half could be said to be entirely normal. Yet it is important to note that only one in this group had evidence of real impairment of kidney function.

In 1927, Boyd (10), in Toronto, reported observations on 150 patients with all types of nephritis, observed from 2 to 5 years after discharge from the hospital. A third of these were classed as acute hemorrhagic nephritis and of these 72 per cent were normal, 12 per cent had died and 16 per cent showed evidence that the disease of the kidney had become chronic. All of those in the last group were

clinically well, however, and the only sign of chronicity was the persistence of a trace of albumin with or without casts in the urine. In the tubular and mixed forms the outcome was not quite so good, and she concluded that the factors influencing the prognosis in nephritis in general were (1) the type of nephritis (acute glomerular offering the best outlook) (2) the age of the patient at the time of the attack (a greater tendency to chronicity in older children) (3) the readiness of removal of foci of infection, and (4) the degree of cooperation of the family in the care of the child. She emphasized the value of renal function tests during convalescence and thereafter as an aid in determining the ultimate prognosis after clinical recovery had taken place.

Most recently, in 1929, in a study of a series of cases of nephritis seen on the Medical Division at Bellevue, Lyttle and Rosenberg (11) reported 4 deaths out of 74 cases of acute glomerular nephritis, two of these having been due to uremia, one to hemolytic streptococcus septicemia and one to pneumonia. Of 38 patients, followed from 1 to 7 years after discharge from the hospital, four had developed a chronic nephritis, and these were patients who had had persistent or recurrent infections. No information is given to indicate the degree of renal damage shown by these patients.

There are recorded in the Harriet Lane files, from the time that the hospital was opened in 1912 to the spring of 1928, 180 cases of acute glomerular nephritis. In 28 of these death occurred, though in only 6 was the nephritis itself the cause. In these 6 cases 3 patients died in the hospital in uremia, one of bichloride poisoning superimposed on an acute nephritis of two weeks' standing (the bichloride having been administered by the grandmother as treatment for the nephritis) and 2 died at home after refusing hospital care. In the remaining 21 cases death was the result of pneumonia, meningitis, congenital syphilis, tuberculosis, rheumatic heart disease and a variety of other infections in which the nephritis was a minor and incidental occurrence during life or only a post-mortem finding. Although the total mortality among the 180 cases is, therefore, 15 per cent, the actual mortality from the nephritis itself is only 3⅓ per cent.

Of the 152 survivors, it has been possible to get back for examination only thirty-four. The remainder were unavailable either be-

cause they were from out of town (22), or could not be located in town (29), or refused to respond to requests to return (31); or they were unsuitable for study because of the inadequacy of the data obtained at the time the diagnosis was made (36).

Among the 34 patients thus assembled for study there was a wide variation in the severity of the attack of nephritis and in the age at which it occurred, so that the group, though small, is a representative one. An effort was made, in each case, to determine the nature of the infection preceding the onset of the nephritis, the severity and duration of the attack, the removal or non-removal of foci of infection after the attack was over, and the number and nature of infections experienced in the interval between the nephritis and the follow-up examination. The examination itself was directed toward the determination of (1) the general physical condition of the patient with special reference to symptoms and signs of kidney disease, and the presence or absence of foci of infection, (2) the state of the cardiovascular system, as indicated by ordinary clinical examination plus blood-pressure determinations, examination of the eye-grounds, and teleoroentgenograms of the chest as a check on the size of the heart, (3) the condition of the urine as ascertained through routine examination of several specimens collected at different times and (4) the state of renal function. This last was determined by means of such tests as it was possible to perform in the out-patient department, *e.g.*, the measurement of 'phthalein excretion, the non-protein nitrogen etc. in the blood, and variations in the specific gravity of the urine. All patients showing any albumin in the urine were tested for orthostatic albuminuria, and those patients showing *any* abnormality on the first examination were seen again six months to two years later and another investigation made, in order to determine whether the abnormality was a constant one and could be regarded as evidence of kidney damage.

Finally, it was hoped that by study at autopsy of the kidneys of children who had died of some other disease but in whom there was a history of acute nephritis sometime in the past, definite evidence as to the presence or absence of residual damage could be obtained. Only one case could be found, however, in which there was a sufficiently long interval between the attack of nephritis and the fatal illness for the result to mean anything.

PATIENT	AGE AT TIME OF NEPHRITIS	TIME SINCE NEPHRITIS	INFECTION ASSOCIATED WITH NEPHRITIS	LABORATORY DATA DURING NEPHRITIS							ONSET TO DISCHARGE FROM HOSPITAL	A
				B.P.	Urine				Renal function			
					Alb.	R.B.C.	Casts	Sp. grav.	Phthal. excretion	Bl. chem. N.P.N.		
									per cent	*mg. per cent*		
1	4 yrs.	1 yr. **3 yrs.**	Ac. tons., cerv. aden.	140/120	++	++	++	1.015	75	25	6 wks.	Still + mos.
2	10 yrs.	2 yrs. **3½ yrs.**	Chr. tons., no ac. inf.	172/105	++	+++	+++	1.018	65	61	3 wks.	Never
3	3 yrs.	2 yrs.	Ac. tons., cerv. aden.	130/70	+	++	++	?	?	27	3 wks.	3 w
4	13 yrs.	2 yrs. **4 yrs.**	Acute pharyngitis	170/120	+++	++	++	1.012	75	27	8 wks.	8 w
5	12 yrs.	2 yrs.	Ac. tons., cerv. aden.	125/90	++	+ (5 wks. after onset)	+	1.023	77	?	In disp. only	12 w
6	5 yrs.	2 yrs.	Cervical adenitis	110/74	++	++ (6 wks. after onset)	—	1.009	?	?	8 wks.	8 w
7	3 yrs.	2 yrs.	Acute tonsillitis	?	+++	+++	++	1.015	?	?	4 wks.	4 w
8	3 yrs.	4 yrs.	Acute tonsillitis	105/78	+++	++ (2 mos. after onset)	++	?	45 (1 hr.)	53	3 mos.	1 y
9	2 yrs.	1 yr.	Op. cleft palate inf.	100/75	++	+++	++	?	?	?	3 wks.	8 w
10	4 yrs.	1½ yrs.	Otitis media	?	++	++	++	1.028	?	31	9 wks.	11 w
11	6 yrs.	2 yrs.	Otitis media	108/68	+	++	++	?	75	?	6 wks.	8 w
12	5 yrs.	2 yrs. **3½ yrs.**	Ac. tons., otitis media	70/44	+	++	+	1.022	68	?	10 wks.	9 w
13	3 yrs.	4 yrs.	Acute tonsillitis	?	History of 2 weeks' nephritis. Seen in Dispensary only							3 w
14	5 yrs.	4 yrs.	Scarlet fever	118/60	+	++	—	?	?	?	2 wks.	2 w
15	3 yrs.	4 yrs.	Ac. tons., cerv. adenitis	120/85	++	+++	+++	1.017	?	?	4 wks.	4 w
16	7 yrs.	4 yrs.	Mastoid infection	115/80	+	++	+	1.020	?	?	6 wks.	6 w
17	5 yrs.	4 yrs.	Acute tonsillitis	?	++	++	+	?	?	?	4 wks.	4 w
18	5 yrs.	4 yrs. **6 yrs.**	Ac. tons., cerv. aden.	110/70	++	++	+	?	?	?	5 wks.	5 w

The patients grouped above the double line are those in whom the nephritis was severe. In those below the line it was mild.
The years indicated in heavy type in the column headed "time since nephritis" represent the time at which a second examination was made because of the finding o
Abbreviations employed in tables: ac. = acute; aden. or ad. = adenitis; adm. = admissions; alb. = albumin; chr. = chronic; cong. = congenital; enl. = enlarged
or rh. = rheumatic; S = severe; sc. fev. = scarlet fever; sev. = several; sl. = slight; sm. = small; subm. = submental; tons. = tonsillitis; T and A = tonsillector

PATIENT	AGE AT TIME OF NEPHRITIS	TIME SINCE NEPHRITIS	INFECTION ASSOCIATED WITH NEPHRITIS	LABORATORY DATA DURING NEPHRITIS						ONSET TO DISCHARGE FROM HOSPITAL	DURATION
				B.P.	Urine			Renal function			Alb.
					Alb.	R.B.C.	Casts	Sp. grav.	Phthal. excretion	Bl. chem. N.P.N.	
									per cent	*mg. per cent*	
1	7 yrs.	6 yrs.	Chr. tons., chr. pneum.	150/120	++	++	+++	1.030	70	?	2 wks.	2 wks.
2	9 yrs.	7 yrs. **8½ yrs.**	Chr. tons., cerv. aden.	128/90	+	+	+	1.026	?	?	8 wks.	8 wks.
3	2 mos.	7 yrs. **9 yrs.**	Congenital syphilis	?	+++	+++	?	?	?	?	3 days	7 wks.
4	9 yrs.	8 yrs.	Acute tonsillitis	?	+++	+ (3 wks. after onset)	+++	?	?	?	7 wks.	7 wks. ?
5	6 yrs.	8 yrs.	Chr. tons., no ac. inf.	154/105	+++	++	++	1.020	45	23.5	4 wks.	4 wks.
6	7 yrs.	12 yrs.	Cervical adenitis	180/130	++	+++	++	?	42	—	8 wks.	5 mos.
7	3 wks.	7 yrs.	Furunculosis	?	++	++	++	?	?	?	5 days	4 wks.
8	5 yrs.	5 yrs.	Chr. tons., no ac. inf.	106/65	+	+	+	1.030	?	?	14 wks.	17 wks. +
9	1 yr.	5 yrs.	Chr. tons., no ac. inf.	?	+	+	—	?	?	?	In disp. only	1 wk. +
10	3 yrs.	5 yrs.	Ac. tons., otitis media	100/58	++	+++	++	1.012	58	?	6 wks.	6 wks. —
11	6 yrs.	5 yrs.	Scarlet fever	?	+	+	+	1.025	?	?	3 wks.	3 wks. +
12	13 yrs.	6 yrs. **7 yrs.**	Ac. tons., rheu. heart	130/90	+	+	+	1.012	53	?	5 wks.	Always a trace
13	6 yrs.	8 yrs.	Osteomyelitis	110/60	+	+	+	1.014	52	?	4 wks.	4 wks. +
14	4 yrs.	8 yrs.	Scarlet fever	116/60	++	++	+++	1.025	50	?	4 wks.	8 wks.
15	8 yrs.	8 yrs.	Scarlet fever	110/35	+	++	++	1.022	?	?	14 wks.	8 wks.
16	6 yrs.	**9½ yrs.** 11 yrs. **12½ yrs.**	Cerv. aden., otitis media	?	++	++	++	1.014	69 I.M.	?	4 wks.	6 wks. +

The patients grouped above the double line are those in whom the nephritis was severe. In those below the line it was mild.
The years indicated in heavy type in the column headed "time since nephritis" represent the time at which a second examination was made because of the findin

TABLE 1

Patients examined less than 5 years after the nephritis

...NSET TO ...SCHARGE FROM ...OSPITAL	DURATION OF		ATTENTION TO FOCI OF INFECTION	INTERVAL HISTORY			
	Alb.	R.B.C.			General condition	Foci of infection	B...
6 wks.	Still + at 6 mos.	6 wks.	T and A immed. after nephr.	Well	Good		80
3 wks.	Never cleared	3 wks.		Well, occ. nycturia	Good	Tonsils, teeth	110
3 wks.	2 wks.	2 wks.	T and A 1 yr. after nephr.	Otitis media, enuresis	Apathetic, under wt.		105
8 wks.	8 wks. +	8 wks. +	T and A 5 yrs. before nephr.	Well	Good	Teeth	120
							110
disp. only	12 wks. +	7 wks.		Well (occ. cold)	Good	Tonsils, cerv. gls.	110
8 wks.	8 wks. +	6 wks.	T and A after nephr.	Frequent colds, occ. nycturia	Fair, chr. eczema	Adenoids, cerv. gls.	100
4 wks.	4 wks. +	3 wks.	T and A after nephr.	Well	Good		65
3 mos.	1 yr.	6 mos.	T and A 2 yrs. after nephr.	Frequent colds	Fair	Cervical glands	90
3 wks.	8 wks.	2 wks.		Recent measles	Fair	Small inf. tonsils	105
9 wks.	11 wks.	8 wks.	T and A after nephr.	Occ. enuresis	Good	Teeth	95
6 wks.	8 wks.	2 wks.	T and A before nephr.	Acute mastoid	Good, rec. mast. op.	Draining mastoid	105
10 wks.	9 wks. +	9 wks. +		Colds in winter	Good, poor posture	Tonsils, teeth	95
	3 wks. −	3 wks. −		Enuresis (always)	Good	Tonsils	100
2 wks.	2 wks.	2 wks.	T and A after nephr.	Measles, pneum., ot. med.	Fair	Bronchitis, teeth	85
4 wks.	4 wks.	3 wks.		Pneumonia (once)	Good	Tonsils	115
6 wks.	6 wks.	4 wks.	T and A before nephr.	Headaches (due to eyes)	Good	Teeth	90
4 wks.	4 wks. +	1 wk.		Frequent colds	Good	Tonsils	93
5 wks.	5 wks. +	4 wks. −	T and A after nephr.	Well	Good	Teeth	95

...use of the finding of albumin on the first examination. The laboratory findings on the second examination are also indicated in heavy type in the appropriate columns.
...ital; enl. = enlarged; ep. or epith. = epithelial; erysip. = erysipelas; full. = fullness; h. = heart; I.M. = intra-muscular; inf. and infec. = infection; mast. = mastoid; M = ...nd A = tonsillectomy and adenoidectomy.

TABLE 2

Patients examined 5 years or longer after the attack of nephritis (Group II)

DURATION OF		ATTENTION TO FOCI OF INFECTION	INTERVAL HISTORY			
Alb.	R.B.C.			General condition	Foci of infection	B.P.
2 wks.	1 wk.		Well	Fair	Tonsils, gen. gland enlargement	105/65
8 wks.	3 wks.	T and A 6 yrs. after nephr.	Ac. tons.; subm. abscess	Good		118/75
7 wks.	7 wks.		Cerv. aden., 1925	Good	Tonsils, teeth	100/60
7 wks. ?	3 wks. +		Ot. media, 1924	Good	Tonsils, teeth	100/70
4 wks.	2 wks.	T and A 3 yrs. after nephr.	Well	Fair	Cervical glands	118/75
5 mos.	4 wks.	T and A before nephr.	Sc. fev., '23; erysip., '28	Good, obese (200 lbs.)		160/90
4 wks.	4 wks.		Impetigo once	Good	Tonsils	105/60
17 wks. +	3 wks.		Frequent colds	Good	Tonsils, teeth	100/75
1 wk. +	5 days +		Well	Good	Tonsils (not bad)	100/70
6 wks. −	4 wks.		Occ. phar. w. cerv. ad.	Good	Tonsils	85/50
3 wks. +	3 wks.		Well	Fair	Tonsils, bad gums	115/65
Always a trace	5 wks.	T and A 8 mos. after nephr.	Sev. adm. (heart)	Rather poor, rh. heart		145/50
4 wks. +	4 wks. +		Well	Good	Teeth	122/54
8 wks.	3 wks. +		Recurrent vomiting	Fair (neurotic)	Tonsils	117/70
8 wks.	12 wks. ? Occ. R.B.C.		Frequent colds	Good	Tonsils	105/65
6 wks. +	6 wks. ?	T and A immed. after nephr.	Pyuria, 1918	Good		115/50

...cause of the finding of albumin on the first examination.

PRESENT EXAMINATION									
	Cardio-vascular			Urine		Renal function			Comment
	B.P.	Fundi	Teleo	Alb.	Mic. exam.	Max. sp. grav. of urine	Phthal. excretion	Bl. N.P.N.	
							per cent	*mg. per cent*	
	80/45	N	N	Trace	Occ. cast	1.010?	60	32	Entirely normal on reëxamination after 2 years
				0	0	1.030	70	28	
	110/65	N	N	Trace	0	1.020	70	32	Status unchanged on reëxamination after 1½ years
				+					
	105/60	N	N	0	0	1.020	85	30	
	120/78	Refrac. error	N	Occ.	Few epith.	1.028	65	37	Still a trace of albumin on reëxamination after 2
	110/78			trace	cells	1.026	75	28	years. In other respects improved
	110/50	N	N	0	0	1.023	70	32	
	100/55	N	N	0	0	1.020	93	35	
	65/45	N	N	0	0	1.028	72	33	
	90/70	N	N	0	0	1.027	87	32	
	105/50	N	N	0	0	1.015	90	36	
	95/60	N	N	0	0	1.030	75	30	
	105/30	N	N	0	0	1.025	85	35	
	95/65	N	N	Ortho-static	0	1.020	90	34	Entirely normal excepting for orthostatic albuminuria. Same after 1½ years
	100/55	N	N	0	0	1.020	85	37	
	85/60	N	Sl. enl. h. cong.	0	0	1.035	80	29	
	115/60	Sl. full veins	N	0	0	1.021	75	30	
	90/30	Refrac. error	N	0	0	1.025	60	36	
	95/60	N	N	0	0	1.026	75	32	
	95/70	N	N	Ortho-static	0	1.020	75	38	Entirely normal excepting for orthostatic albuminuria. Same after 2 years

...oid; M = mild; N = normal; nephr. = nephritis; occ. = occasional; op. = operation; ot. = otitis; phar. = pharyngitis; rec. = recent; refract. = refractive; rheu.

PRESENT EXAMINATION								
	Cardio-vascular		Urine		Renal function			Comment
...P.	Fundi	Teleo	Alb.	Mic. exam.	Max. sp. grav. of urine	Phthal. excretion	Bl. N.P.N.	
						per cent	*mg. per cent*	
.../65	N	N	0	0	1.025	70	33	
.../75	N	N	Ortho-static	0	1.035	75	28	Entirely normal excepting for orthostatic albuminuria. Same after 1½ years
.../60	N	N	+	0	1.019	75	24	Status unchanged on reëxamination after 2 years
.../70	Discs sl. hazy	N	0	0	1.035	60+	31	
.../75	Refract. error	N	0	0	1.028	65	33	
.../90	Sl. full. of veins	N	0	0	1.025	70	36	
.../60	N	N	0	0	1.018	75	22	
.../75	N	N	0	0	1.021	65	33	
.../70	N	N	0	0	1.025	70	33	
.../50	N	N	0	0	1.030	65	30	
.../65	Sl. refract. error	N	0	0	1.019	70	27	
.../50	Pulsating veins	Enl. h. (rheum.)	Trace	0	1.020	65	27	Rheumatic heart with aortic and mitral insufficiency. Always slight decompensation
.../54	N	N	0	0	1.021	70	33	
.../70	N	N	0	0	1.022	75	32	
.../65	Sm. arter. sl. tortuous	N	Trace	0	1.025	85	24	Status unchanged on reëxamination after 1½ years
.../50	N	N	Trace	Occ. W.B.C., few ep. cells	1.035	65	26	Status unchanged on reëxamination after 1½ years

The ages at which the nephritis occurred ranged from 3 weeks to 13 years. There were 4 patients under 2 years of age, 24 between 3 and 7 years, and 6 over 7 years. On the basis of a combination of severity of symptoms with edema, elevated blood pressure and marked urinary changes 15 of the 34 patients may be said to have had severe attacks, while the remaining 19 may be said to have had mild attacks, though in a large proportion of them the changes in the urine were as marked as in the others. The interval between the attack of nephritis and the follow-up examination varied from one to twelve years. In 18 cases the interval was less than 5 years, in 16 it was 5 years or more. The results of the examinations are tabulated in the following pages, those patients who were seen within five years being grouped in one table (Table 1) and those seen after the longer interval in another (Table 2). Similarly, within each table, the patients whose nephritis was severe are grouped together above those in whom it was mild, so that the outcome in the severe and the mild cases can be compared at a glance (*cf.*, Tables 1 and 2).

All of the 34 patients are symptomatically well at the present time with the exception of one who has advanced rheumatic heart disease; in any who are at all below par physically adequate explanation is found outside the urinary tract. The heart is enlarged in only two, one of whom has a rheumatic infection of the heart and the other a congenital malformation of the heart. The blood pressure is very high in two, the girl (145/50 at the age of thirteen years) with the rheumatic heart disease who has both a mitral and an aortic insufficiency and the boy (160/90 at the age of nineteen years) who is extremely obese. These pressures are both adequately accounted for by factors unrelated to the previous nephritis. The boy with the pressure of 160/90 has not even as much as a trace of albumin in the urine to point to any renal disturbance. In two of the other children the systolic blood pressure is a little above the average for their ages, 115/60 at seven years and 122/54 at fourteen years. In the absence of any abnormal urinary findings and of any renal impairment indicated by renal function tests in these particular patients, no real significance can be attached to this point. The elevation is certainly not marked and there has been no further increase in blood pressure in these patients during the two years since this examination was made.

Urinalysis reveals albuminuria in 9 patients—four in group I (those who had nephritis less than five years ago) and five in group II (those who had nephritis more than five years ago). Of the four in group I, two have only an orthostatic albuminuria. In the other two the albuminuria is present under all circumstances, and the previous nephritis is the only explanation that can be found for it. Of the five in group II, one has an orthostatic albuminuria. Another has advanced rheumatic heart disease, with which there is always a degree of decompensation. As there was no sign of active rheumatic infection at the time of the first follow-up examination and no history of any during the interval between that and the re-examination a year later, her albuminuria is best explained on the basis of circulatory insufficiency. In the remaining three there are no extraneous factors to account for the albuminuria, which may, therefore, be attributed to the previous nephritis. In none of the patients with orthostatic albuminuria is it possible to determine whether or not this antedated the nephritis. In the two in group I the orthostatic albuminuria was not noted until the present examination; in the single patient in group II it was discovered after he was out of bed during the period of convalescence from his nephritis. This boy had a recurrence of his nephritis associated with a submental abscess two years after the initial attack, as indicated by the persistence of albumin at that time even in the recumbent position and the reappearance of casts in the urine. This lasted only a few days and he is the only one of the thirty-four patients studied who has a record of any such recurrence.

The study of renal function in these patients necessitates a brief consideration of the figures characteristic of normal children for 'phthalein excretion, non-protein nitrogen, uric acid and creatinine of the blood, and variations in specific gravity of the urine. In evaluating our results we have regarded as normal a two-hour 'phthalein excretion of at least 60 per cent (most of which is excreted during the first hour), a blood non-protein nitrogen of less than 40 mg. per cent, creatinine of less than 3 mg. per cent and uric acid of less than 4.0 mg. per cent and a variation in specific gravity of the urine of at least nine points with the ability to attain a maximum concentration of at least 1.020. These figures are in accord with the values obtained in the few investigations that have been made on normal children and on

children free from renal disease, but in hospitals from various other causes. A summary of these studies is tabulated below:

TABLE 3

Measurements of phthalein excretion, and non-protein nitrogen, uric acid and creatinine of the blood in children with normal kidneys, as given in the literature

AUTHORS	PHTHALEIN EXCRETION	N.P.N.	URIC ACID	CREATININE
	per cent	*mg. per cent*	*mg. per cent*	*mg. per cent*
Tileston and Comfort (12), (5 cases)	78–81	20.2–34		
Leopold and Bernhard (13), (50 cases)	50–96 (Av. = 70)	(?)–40 (Av. = 28)	0.6–3.2 (Av. = 1.8)	0.5–4 (Av. = 1.5)
Hill (14), (27 cases)	64–100			
Wilcox and Lyttle (15), (91 cases)	60+	16–37 (Av. = 27.5)	1–3.8	1–1.5

According to these standards all of our 34 patients showed a normal 'phthalein output with a two-hour excretion ranging from 60–93 per cent, and an average of 74 per cent.

Similarly, the blood chemistry determinations gave normal results in all. Non-protein nitrogen, uric acid, creatinine and chloride determinations were made in every case. The non-protein nitrogen ranged from 22–38 mg. per cent with an average of 30 mg. per cent, the uric acid from 1.8–3.6 mg. per cent with an average of 2.4 mg. per cent, the creatinine from 1.0–1.9 mg. per cent with an average of 1.3 mg. per cent and the chloride from 452–651 mg. per cent with an average of 507 mg. per cent. Since these values are all well within normal limits, only the non-protein nitrogen values have been included in the tables as representative of the blood findings.

The specific gravity of the urine showed adequate variation in all of the patients, but four of them failed to reach a maximum of 1.020. As the collection of specimens had to be carried out largely at home, and it was necessary to depend on the intelligent co-operation of both mother and child in order to accomplish the necessary restriction of fluids during the period of collection, it was not always possible to

make a satisfactory test. The one child whose urine failed to give a specific gravity reading above 1.015 was a small girl from whom only two specimens sufficient in quantity for a specific gravity determination could be obtained in the dispensary. She finally moved and was lost sight of before the examinations could be completed. Of the other three patients whose urine did not quite attain the desired goal of concentration one reached a specific gravity of 1.018 and two 1.019, and it seems probable that the specific gravities would have exceeded these values, could enough specimens have been obtained. Certainly there is not sufficient evidence on which to assume that the kidneys of any of these patients showed a real inability to concentrate satisfactorily.

The results of the kidney-function tests indicate, therefore, that none of the 34 patients examined has any demonstrable impairment of renal function, and that albuminuria is the only finding that points to possible kidney damage in some, even though in three of these the attack of nephritis occurred as long ago as seven, eight, and even eleven years. This leaves us then with the following summary of our data:

TABLE 4

Results of examinations of patients with history of acute nephritis in writer's series of cases

NUMBER OF PATIENTS	PRESENT STATUS
25 (73.5 per cent)	Unquestionable complete recovery[2]
3 (8.8 per cent)	Orthostatic albuminuria which is not necessarily attributable to the previous nephritis, and may well be entirely independent of it
1 (3 per cent)	Rheumatic heart disease; a constant trace of albumin, which is explicable on the basis of a mild degree of circulatory insufficiency
5 (14.7 per cent)	Albuminuria for which the previous nephritis is the only explanation that can be found. Three of these patients have never shown more than a trace of albumin, but the other two consistently show a definite "one +" albumin

[2] The words "complete recovery" are used throughout this paper to indicate that, in addition to symptomatic recovery, complete clearing of the urine has also taken place.

All the patients, however, are symptomatically well and leading normal lives with the exception of the one whose rheumatic heart disease is so advanced that some restriction of activity is necessary.

With regard to the one boy in whose case an autopsy was performed several years after his attack of nephritis the results are equally encouraging from the point of view of the kidneys. At the age of eight years this boy had a fairly severe attack of nephritis from which he made a clinical recovery in six weeks. Four years later he died in the hospital of rheumatic heart disease with an acute pericarditis as the terminal event. At the autopsy the kidneys showed, grossly and microscopically, some evidence of a mild fresh acute nephritis associated with the terminal illness, but in the microscopic sections, still available for examination, there are no changes, no scarring of any kind to indicate that any kidney damage had resulted from the initial nephritis four years previously.

For the purpose of convenience in analysis, the four patients in group I and the five in group II showing albuminuria have been grouped together in a table (table 5), where the results of their renal function tests can be compared with those obtained on the patients whose urine was normal in each group. It will be seen that there is practically no difference. Included, also, in this table are data in regard to a number of points investigated in the effort to determine what factors, if any, influence the prognosis in nephritis, why some patients fail to make a complete recovery, while others show no trace of the illness through which they have passed. A discussion of the points investigated follows:

1. Age at which the nephritis occurs. In each group the average age of those patients now showing albuminuria was slightly higher at the time of the nephritis than was that of the patients now normal. Furthermore, when the patients are grouped according to age, we find that the incidence of albuminuria is much higher in those patients in whom the nephritis occurred at eight years or later, than in those in whom it occurred at seven years or earlier. The relative proportion in the older and younger groups remains the same, whether the "orthostatic" and the "rheumatic" patients are included among those whose kidneys are believed to have *suffered* damage from the nephritis or whether, since their albuminuria may be due to other

TABLE 5

Analysis of the patients now showing albuminuria as compared with those who are normal

	Age at time of nephritis	Interval since nephritis	Severe or mild	Duration of hospital stay	Urine on discharge	Duration of albumin	Duration of R.B.C.	T and A	Interval infection	Renal function: Urine—max. sp. gr.	Renal function: Phthalein excretion	Renal function: Blood, N.P.N.
Group I												
											per cent	*mg. per cent*
1. Patient 12 (orthostatic)	5 yrs.	2 yrs.	M	10 wks.	Tr. alb.		9 wks.	0	0	1.020	90	34
2. Patient 18 (orthostatic)	5 yrs.	4 yrs.	M	5 wks.	Tr. alb.	5 wks. +	4 wks.	+	0	1.020	75	32
3. Patient 2	10 yrs.	2 yrs.	S	3 wks.	+ alb.	5 wks. +	3 wks.	0	0	1.020	70	28
4. Patient 4	13 yrs.	2 yrs.	S	8 wks.	Tr. alb.		8 wks. +	+	0	1.028	75	32
Average	**8¼ yrs.**	**2¼ yrs.**		**6½ wks.**			**6 wks.**			**1.022**	**78**	**31½**
Variations among the 14 normal patients	2 yrs. to 12 yrs.	1 yr. to 4 yrs.	8 M 6 S	2 wks. to 12 wks.	4 = clear 10 = alb. 1 = R.B.C.	3 wks. to 1 yr.	2 wks. to 6 mos.	7 = + 7 = 0	9 = + 5 = 0	1 = 1.015 13 = 1.020 to 1.035	60–93	29–38
Average	**5½ yrs.**	**2.7 yrs.**		**5½ wks.**		**11 wks.**	**5 wks.**			**1.024+**	**78**	**32½**
Group II												
1. Patient 2 (orthostatic)	9 yrs.	7 yrs.	S	8 wks.	+ alb.		3 wks.	+	+	1.035	63	28
2. Patient 12 (rheumatic)	13 yrs.	6 yrs.	M	5 wks.	Tr. alb.		5 wks.	+	+	1.020	65	27
3. Patient 3	2 mos.	7 yrs.	S	3 days	Alb. + R.B.C.	12 wks.	7 wks.	0	+	1.019	75	24
4. Patient 15	8 yrs.	8 yrs.	M	14 wks.	Clear		12 wks.	0	+	1.025	85	24
5. Patient 16	6 yrs.	11 yrs.	M	4 wks.	+ alb.	8 wks.	6 wks.	+	+	1.035	65	26
Average	**7 yrs.**	**8 yrs.**		**6 wks.**			**6½ wks.**			**1.026**	**70½**	**26**
Variations among the 11 normal patients	3 wks. to 7 yrs.	5 yrs. to 12 yrs.	6 M 5 S	1 wk. to 14 wks.	2 = clear 9 = alb. 1 = R.B.C.	1 wk. to 5 mos.	1 wk. to 5 wks.	2 = + 9 = 0	6 = + 5 = 0	1.018–1.035	60–75	22–36
Average	**5 yrs.**	**7 yrs.**		**5 wks.**		**7 wks.**	**3 wks.**			**1.033**	**69½**	**29**

factors, they are included among those whose kidneys *escaped* damage from the nephritis. When grouped thus, according to age, the results are as follows:

TABLE 6

Cases in which albuminuria was found, analyzed according to age

AGE GROUP	TOTAL NUMBER OF PATIENTS	NUMBER WITH ALBUMINURIA
(1) 2 yrs. or less	4	1
(2) 3–7 yrs.	24	3 (includes 2 patients with orthostatic albuminuria)
(3) 8 yrs. or more	6	5 (includes one patient with orthostatic albuminuria and the patient with rheumatic heart disease)

This analysis leaves the impression that the incidence of nephritis is higher among younger children and that the prospect of complete recovery is greater the younger the patient at the time of his nephritis. The number of cases is, however, too small to warrant any positive conclusion in this regard.

In the youngest group the one patient who now shows albuminuria is the one whose nephritis occurred as a complication of congenital syphilis when he was two months of age. As so few babies with this combination of diseases survive, he should probably be considered in a class by himself. We believe, however, that he had a true glomerular nephritis secondary to the upper respiratory infection that so commonly accompanies "snuffles," and not a so-called syphilitic nephritis. He is entirely free from any evidence of syphilis now at the age of seven, and his Wassermann has been negative since he was nineteen months of age.

2. Type of infection preceding nephritis. Upper respiratory infections, including otitis media and mastoiditis, predominate as the precursors of the nephritis. Scarlet fever was responsible in only four cases. Furunculosis occurred in one (the three weeks old baby), osteomyelitis in one, and there was the one patient with congenital syphilis in whom there was, also, upper respiratory infection associated with the "snuffles." Only four patients failed to show evidence or give a history of recent acute infection, but in all of these there was undoubted chronic infection of the tonsils.

In the patients continuing to show albuminuria, scarlet fever was the infection that preceded the nephritis in only one. Upper respiratory tract infection complicating congenital syphilis, as already described, was responsible for another. One patient was among those who failed to show evidence of acute infection, while simple acute upper respiratory infections appeared responsible for all the rest. No one type of infection can, therefore, be blamed more than another. Certainly scarlet fever, which is thought to be more often responsible for a persistent nephritis than is a simple tonsillitis or pharyngitis, contributed no more than its relative share in this series of cases.

3. Severity of the attack of nephritis. This has apparently made no difference in the prognosis. In 5 of the 9 patients with albuminuria, the attack was mild. In the 25 patients now entirely normal, the attack was mild in 14, whereas one of the eleven in whom it was severe was in uremia for several days. Whether the attack is severe or mild, therefore, once the acute stage is passed, there appears to be about the same chance for complete recovery.

4. Duration of hospital stay. This again appears to have had no definite influence on the outcome. The vast majority of all patients still showed albumin at the time of discharge from the hospital, and those now normal averaged a week less in the hospital than the others.

5. Duration of albuminuria and hematuria. As indicated above, most of the patients—in fact all but 6 of the entire 34—still showed albuminuria at the time of discharge from the hospital, and 3 still showed red blood cells in the urine. In general, the urine of the majority of those who recovered completely cleared promptly within eight or nine weeks, but in three the albumin persisted as long as four to twelve months. Another whose urine showed a trace of albumin and an occasional cast on our follow-up examination one year after her nephritis, has been found on re-examination two years later to be entirely normal without even an occasional trace of albumin. In some of those now showing albuminuria, the albumin never disappeared. In others, and this includes three of the five who now show albuminuria under all circumstances, it apparently disappeared in five to twelve weeks, only to reappear, although an occasional trace may have been overlooked in the earlier examinations.

The red blood cells disappeared from the urine fairly promptly in

all patients. In the majority they had gone within a month, and in only three were they present for longer than two months. One, in whom they persisted for nine weeks, is the first patient in group I with orthostatic albuminuria. Another, in whom they lasted for twelve weeks, is the patient in group II with post-scarlatinal nephritis, who now shows a persistent albuminuria. The third, however, whose urine contained red blood cells for six months and albumin for a year has now entirely normal urine four years after his nephritis, with a 'phthalein excretion of 87 per cent, which is well above the average.

From all this one concludes that the prognosis is slightly more uncertain if albumin and red cells persist for a long time, and yet complete recovery is still possible even when they persist for months.

6. Attention to foci of infection. Consideration of the number of patients who have had tonsils and adenoids removed affords the most tangible approach to this question. Half of those patients now considered abnormal have had this attention, while more than half of those now entirely normal (in fact all but two in group II) have not had tonsillectomy. The outcome might have been better, had this been looked after in every case and it might have been worse, had it been neglected in all. Yet, it is interesting that sixteen patients in whom no attempt was made to eradicate foci of infection are now entirely normal. In fact, on the present examination only four of the normal patients have been found entirely free from any focus of infection, for many have bad teeth even though otherwise perfectly well. On the other hand, three in the abnormal group are free from any discoverable focus of infection.

7. Number and type of infections during the interval since the attack of nephritis. Here, again, the results are equivocal, as none of the albuminuric patients in Group I has had any interval infection of consequence, while all of those in Group II have. On the other hand, of the 25 patients now entirely normal, 15 have had intercurrent infections. One of them even went through two streptococcal infections, scarlet fever and erysipelas, without a recurrence of his nephritis or any subsequent damage. Only one patient in the entire group, as far as we know, has had a recurrence of his nephritis with a second infection and that is the patient in Group II with orthostatic albuminuria who had a recurrence during the course of a submental abscess,

but who recovered again entirely excepting for the orthostatic condition and now shows excellent kidney function with a 'phthalein excretion of 75 per cent.

The implication is that children who have once had an acute nephritis stand subsequent infections just as well as children who have not had nephritis, and show no greater susceptibility to kidney involvement the second time.

It is apparent, then, that very few of the factors investigated had any influence whatever on the final outcome of the nephritis in this small group of children. The age is the only factor that seems to have made any real difference in these patients, complete recovery having occurred in a higher percentage of the younger children. The promptness with which the urine clears is apparently of some immediate prognostic import, and it is probable also that attention to foci of infection is of some importance in bringing about a favorable result, although our statistics fail to demonstrate this with any certainty, as albuminuria is still present in three patients who are entirely free from any apparent focus of infection, and many who were neglected on this score now have perfectly normal kidneys. In general, one is left with the impression that in children there is a marked tendency toward complete recovery "no matter what."

SUMMARY

A study is presented of 34 patients examined one to twelve years after an attack of acute glomerular nephritis. Eighteen (Group I) were seen less than five years and sixteen (Group II) more than five years after the nephritis.

All, excepting one girl with advanced rheumatic heart disease, are symptomatically well and are leading normal lives.

Nine patients show albuminuria, 4 in Group I and 5 in Group II. Three of these have only an orthostatic albuminuria. Another, with an advanced rheumatic heart disease, shows a constant trace of albumin which can be explained on the basis of circulatory insufficiency, as a mild degree of cardiac decompensation is always present. This leaves 2 in Group I and 3 in Group II who show persistant albuminuria which, in the absence of other causes, may be attributed to the nephritis. In one of the latter, eleven years have passed since the nephritis.

None of the patients in whom examination was satisfactory shows any impairment of kidney function. In all of the patients with albuminuria the level of function is well above that regarded as the lower limit of normal, while the average for them as a group is as high as that for the patients found to be entirely normal. Furthermore, re-examination of the abnormal group six months to two years after this first follow-up examination, has shown no change in the status of the kidneys.

A study of the records of those patients who had died revealed one patient who came to autopsy four years after an attack of acute nephritis. His kidneys showed no trace, either macroscopically or microscopically, of his previous nephritis, although there was evidence of a mild fresh acute nephritis which was associated with his terminal illness.

All but six of the patients were seven years of age or less at the time of their nephritis. The percentage of these patients now showing albuminuria is definitely less than the percentage of those in whom the nephritis occurred at an age beyond seven.

The type of infection preceding the nephritis has had little influence on the outcome. Only one of the four patients in whom it followed scarlet fever is among those found to be abnormal. Also, among the abnormal patients is one who had an acute nephritis complicating congenital syphilis at the age of two months.

The severity of the nephritis and the duration of the patient's stay in the hospital do not seem to have influenced the prognosis.

In the majority of those patients who are now normal the urine cleared quite promptly; in most within two months. In several, however, complete clearing took place even after the albumin had persisted for many months. These have had no recurrence of their trouble.

In 20 patients foci of infection were not eradicated following the nephritis. Sixteen of these are among the 25 patients who are now entirely normal in all respects. Five more of the normal patients have some other focus of infection, at least in the teeth, so that only four are entirely free of *any* focus. Three of the nine albuminuric patients are *without* discoverable foci of infection.

Fifteen of the normal patients have passed through subsequent in-

fections without a recurrence of their nephritis and this includes one in whom scarlet fever and erysipelas were the infections experienced. The four albuminuric patients in Group I have had no intercurrent infections.

Only one patient in the entire group has had a real recurrence of his nephritis with a subsequent infection and that patient is now normal except for an orthostatic albuminuria.

CONCLUSIONS

From the above analysis one cannot escape the conclusion that in acute glomerular nephritis in children the prognosis is good, and, in general, the younger the child, the better the prospect of complete recovery. Even when the urine fails to clear entirely, albuminuria may persist for years without impairment of general health or kidney function. It may also disappear completely after it has been present at least as long as a year. Children who have once had acute nephritis stand subsequent infections without greater liability to complicating renal disease than is shown by children who have never had nephritis.

Although many of the patients are now entirely normal in spite of neglect of foci of infection following the attack of nephritis, the fact that several of those now showing some abnormality are among those neglected makes one feel that it is wise to attend to such foci promptly in all cases. This has been done routinely in the Harriet Lane Home during more recent years and an effort is being made to accomplish it on these patients now.

If is of the utmost importance, as well as of interest, to continue to follow these patients with albuminuria in order to determine the ultimate prognosis in each case. From the results of these examinations it seems quite possible that some may yet clear entirely, and that those who fail to clear will continue to do well for many years in spite of the albuminuria.

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ON THE PATHOLOGY AND PATHOGENESIS OF SCLERODERMA

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Apart from changes in the skin and peripheral vessels little is known as to the pathology and more especially the pathogenesis of diffuse scleroderma. The following case would appear to be of more than usual interest because it shows lesions of the sympathetic nervous system in a case presenting all the changes characteristic of scleroderma.

R. G. 30 years, female, white. She was first seen November 4, 1919, when she complained of general stiffness in all her joints, "hardness" of the fingers and a dry scaly skin. All this had been coming on for three or four years. The family history was without import. She had had bronchopneumonia as a child and later rheumatism of one wrist.

About three and a half years before, in the winter, her hands began to be very cold, and blue or blanched. The following summer these symptoms were better but recurred that winter and each subsequent one. One and a half years before she came to the clinic she noted that the skin was becoming hard at the tips of the fingers, over the knuckles and over the elbows. These places became tender and cracked open. In the summer of this year, 1919, a diagnosis of Raynaud's disease was made. Stiffness of the joints began to appear and she noted mottled discoloration of the skin. She began to have a tight feeling in the throat. The mouth and skin felt drawn, the lips were stiff. Pressure over the skin of the forehead left pitting.

On examination she was slightly below the normal weight. The skin over the face was oily, smooth and thick, being tightly drawn over the bones. The skin surfaces of other parts of the body, especially hands and forearms, showed the same changes. There were areas of pigmentation, especially over the neck. The tips of the fingers showed some scarring, and x-ray showed destruction of the tips of the phalanges. The finger-nails were thick, brittle and ridged. The x-rays of the gastro-intestinal tract were normal at this time but for some caecal retention. Wassermann negative. X-ray of the sella turcica showed it to be greatly decreased in size.

In December, 1919, her adenoids and tonsils were removed and she was given thyroid and pituitary extract.

In May, 1923, she was seen again. She had lost a little weight. The skin changes had progressed somewhat; there was more destruction of the fingers, and she was beginning to suffer from attacks that suggested spasm of the oesophagus. Contraction of the lower end of the oesophagus was confirmed by x-ray examination.

In October, 1927, the changes in the skin, especially those of the fingers, had still further progressed. The oesophageal symptoms were somewhat relieved.

On July 10, 1929, she was admitted to the hospital on account of a gastro-intestinal upset. This had begun ten days before with pain in the epigastrium and diarrhoea. She had had a similar attack about four months before.

The changes in the skin everywhere had advanced since she was last seen, although perhaps less in the fingers than elsewhere. Examination at this time showed constant occult blood in the stools. X-ray of the stomach showed some obstruction at the pylorus. Both small and large intestines were dilated and there seemed to be an almost complete obstruction of the descending colon. She was transferred to the Surgical Service.

On August 30, 1929, an operation was performed. The colon was found to be enlarged and filled with putty-like masses. An ileo-sigmoidostomy was performed. The diarrhoea persisted and there was frequent vomiting. On September 16th another operation was performed and a caecostomy done. A section of skin removed at this operation showed changes characteristic of scleroderma with pigmentation. She did not improve and died on September 22nd, at 8:35 p.m. An autopsy was performed at 8:45 the next morning—that is, twelve hours later.

Autopsy No. 11115. Anatomical Diagnosis: Scleroderma, leucoderma, Raynaud's disease with destruction of tips of fingers. Dilatation of oesophagus and colon without mechanical obstruction. Abdominal incision for laparotomy and caecostomy. Ileosigmoidostomy with drainage of caecum. Lobular pneumonia. Acute and chronic pleurisy. Peculiar induration of areas of lung showing widened bronchioles and alveoli, with pneumonic consolidation. Changes in cells of sympathetic ganglia. Old rheumatism with pericarditis, myocarditis, mitral stenosis and tricuspid thickening. Emaciation. Cysts in kidneys. Aberrant gall-bladder. Groups of fat cells in spleen. Chronic ulcerative oesophagitis.

General Appearance. The body shows extreme emaciation,—the weight being only 37.5 kilograms. This appearance of emaciation is accentuated by the tight and shiny skin which is present over most parts of the body, more especially over the face and bony prominences. The head and face, besides the peculiar tenseness of the skin, show patches of brown pigmentation contrasting sharply with surrounding depigmented areas. The eyelids are drawn apart apparently by the contraction of the waxlike skin; so also are the lips, but here there are in addition surrounding depressed and puckered scars. The pupils are unequal—the left is smaller than the right, eccentric and irregular. The hair is scanty and mostly grey. The hands and the feet show very marked changes. These are most marked over the dorsum of the left hand. Here the skin is tightly drawn over the underlying metacarpals and is shiny. Patches of brown pigmentation and white depigmented

areas contrast sharply with each other. The finger-tips are blue and scarred. In the case of the middle finger the whole of the terminal phalanx and the overlying tissues as far proximal as the root of the nail have been lost. The other fingers show varying but lesser amounts of this necrosis, scarring and disappearance. The toes of both feet, especially the fourth and fifth, show bluish-mauve discoloration with some scarring. Disturbances in pigmentation similar to those already mentioned are found over all bony prominences. The skin over the abdomen, chest, and legs shows areas of wax-like skin and otherwise a general brown pigmentation. There is no oedema.

Heart: The heart weighs 260 grams. Tricuspid ring 12 cm.; pulmonary ring 7 cm.; mitral ring 9 cm.; aortic ring 6 cm. Wall of right ventricle 4 mm.; wall of left ventricle 14 mm.

The heart is rather small. Over the anterior surface of the left ventricle is a patch of fresh pericarditis and some older patches of epicardial thickening. The margins of the tricuspid leaflets are slightly thickened and rolled, while the chordae tendineae are short and thick, but there is no sign of fresh inflammation. The pulmonary cusps are normal. The mitral leaflets show even more thickening at the edges than do those of the tricuspid; also, the chordae are very definitely thickened and shortened. On the posterior mitral leaflet there is a small, fairly recent, pin-head vegetation. The aortic cusps are normal. No macroscopic changes can be recognised in the myocardium.

Lungs: The left lung shows some old thickenings of the pleura and fibrous adhesions over the upper lobe. Over the lower lobe there is a little fresh granular pleurisy and there are quite extensive areas of consolidation.

The right lung shows similar changes over the pleura of the upper lobe. The lower lobe is extensively consolidated and its surface covered by a thin granular layer of fibrin, some of which is of very recent appearance. Within the confluent consolidated tissue of the lower lobe can be seen opaque yellow patches, round in outline and some 2 mm. in diameter, with denser consolidation around them. Some of the pneumonic process appears older; it is grey and a little translucent; the alveoli are dilated and apparently contain some purulent exudate. The appearances suggest organisation.

Intestinal Tract: The pharynx is normal. At the level of the cricoid cartilage the oesophagus widens out, and 1 cm. below this level measures 4.5 cm. in circumference. At the level of the bifurcation of the trachea the circumference measures 5 cm. and at the cardia 5.5 cm. There is no narrowing at the actual orifice into the stomach. From the arytenoid cartilages to the cardia the oesophagus measures 29 cm. in length. The muscular coats of the wall are not visibly hypertrophied. The mucosa over the lower three-fifths is apparently lacking. The upper margin of this change is not sharply defined but is beset by isolated islands of mucosa which are white, opaque and heaped up as though perhaps composed of regenerating epithelium.

The stomach is a little dilated as are the loops of small intestine, but they show no other abnormality. The lower end of the ileum has been cut across. The prox-

imal loop has been inserted into the wall of the sigmoid colon, while the distal has been closed off. As a result the caecum has been converted into a cul-de-sac drained by a caecostomy.

The whole of the large intestine is markedly dilated. There is no evident hypertrophy even toward the lower end but it is considered that the degree of dilatation would suffice to mask hypertrophy of slight extent.

Liver: There is a small cavity, about 1 cm. in length, lined with a greenish mucosa and filled with bile, lying outside the liver but within the capsule, on the diaphragmatic surface just to the right of the falciform ligament. The liver itself appears normal externally and on section.

Adrenals: Macroscopically show nothing abnormal.

Genito-urinary Apparatus is normal throughout.

Thyroid shows no abnormality.

The spinal cord and sympathetic chains, together with the brachial and lumbar plexuses, appear normal in the gross but are taken for section. Examination of the brain is not permitted.

The other organs show nothing of note.

Microscopical Appearances. The Skin: Sections are prepared from several regions. *From the right elbow:* the epidermis is thin and there is perhaps a little more keratinisation than normal. The papillary projections down into the corium are very infrequent and those that are present are small and atrophic. The rete Malpighii contains abundant brown pigment, the distribution of which is quite irregular so that some places are entirely devoid of it. The dermis is occupied by dense scar tissue in the form of interlacing hyaline fibres and is poor in cells. This hyaline connective tissue extends in strands into the subdermis between the somewhat atrophied fat lobules. There is no sign of inflammation. As already mentioned, cells are few and what are present are the wandering cells usually seen in the neighborhood of vessels. The smaller arteries in the dermis show somewhat thickened walls due to a proliferation of the intima and endothelium, but nowhere is the lumen occluded. The sweat glands are small and atrophic. There are no sebaceous glands or hair follicles.

From the left shoulder: In this section atrophic papillae are rather more frequent. The melanotic pigment is more abundant and is found also in the upper layers of the dermis below the more heavily pigmented areas of the rete Malpighii. It is mostly contained within mononuclear cells, although some lies free, and is in close relation to the smaller lymphatic vessels. In the dermis the scar tissue is dense and a stain for elastic fibres shows these to be very plentiful amongst the connective tissue. There are a few hair follicles and sebaceous glands. The sweat glands are very atrophic (Fig. I). The musculi arrectores papillae are hypertrophied and appear as conspicuous bands (Fig. II). The vessels show the same endarteritis as before and there is apparently some proliferation of the elastic fibres.

From the abdomen: The changes here are similar in nature but less in degree than those already described. Papillae are more evident and the pigmentation is less

although there still are accumulations around the lymphatics in the upper layers of the dermis. The sweat-glands are better preserved; hair follicles and sebaceous glands are plentiful. The arrectores papillae show some hypertrophy. The scarring of the dermis is less marked and does not extend into the subdermis. A fragment of the rectus abdominis included in the section appears normal.

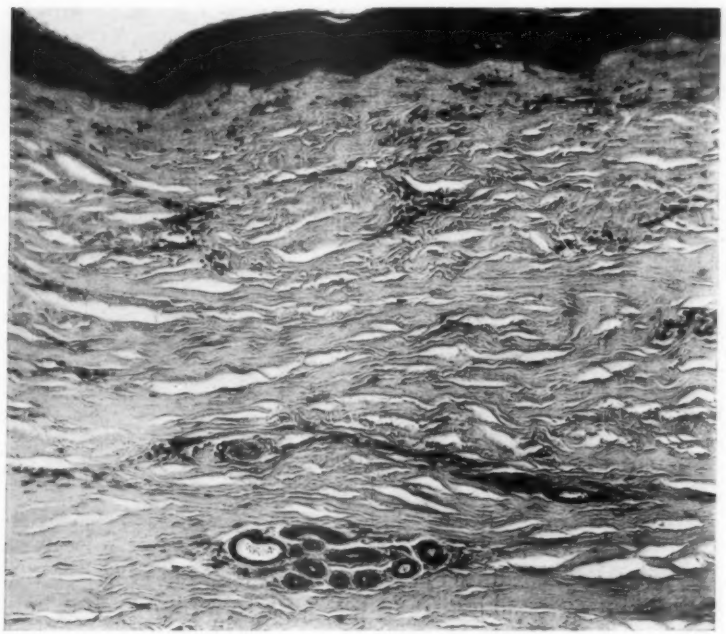

FIG. I. SECTION OF SKIN

The absence of papillae is apparent. Atrophic sweat glands are surrounded by a densely scarred and almost hyaline dermis.

From the thigh: The appearances are those of the skin from the abdomen.

From the chest: Here again the changes are similar to those in the last two, except that in this case there are present more abundant cells, chiefly monocytes and lymphocytes, especially around the vessels of the dermis.

A section of skin stained to show the myelin sheaths shows these to be normal, although perhaps the nerve filaments are less numerous than usual.

Voluntary muscle from the thigh: The muscle presents a peculiar appearance.

Shrunken hyaline and dark-staining fibres lie intermingled with fibres which are swollen, pale and apparently distintegrated so that individual fibrils are plainly seen. The cross striations can still be seen in the shrunken fibres but not in the swollen ones. The nuclei of the sarcolemma sheaths around the former are approximated and appear as nearly continuous lines; some of these fibres are tortuous and curled. There are a few apparently normal fibres (Fig. V). The smaller arteries show intimal proliferation of varying degree.

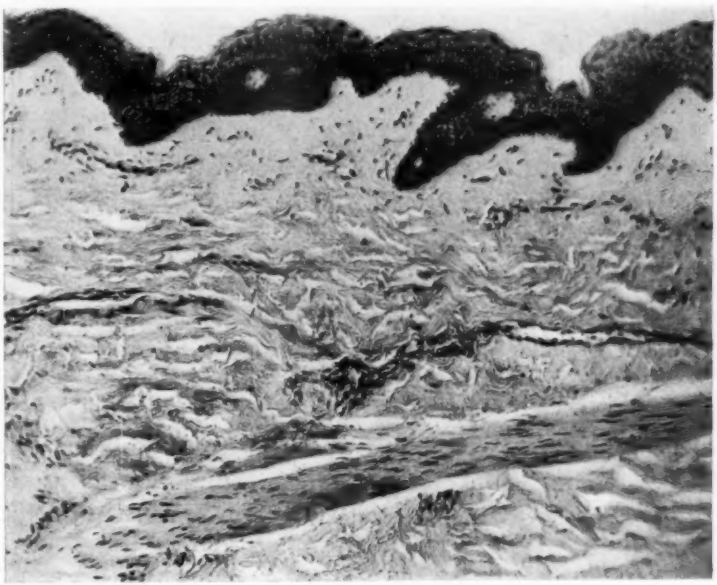

FIG. II. SECTION OF SKIN

In general the changes are similar to those in Fig. I. An hypertrophied band of smooth muscle runs through the dermis.

Heart: There is some thickening of the endocardium. The mitral valve is scarred, thickened and shows accumulations of cells. There are scars in the myocardium and some subacute pericarditis.

Lungs: There is some fresh lobular pneumonia. The process at the base of the left lung reveals itself as a process of scarring with widening of bronchi, bronchioles and alveoli. These are filled with exudate, some of which is very fresh and composed of polymorphs, often disintegrating, surrounding masses of bacteria;

other parts of the exudate are commencing to organize. There is a striking metaplasia of the bronchial epithelium which is in many places stratified in type.

Spleen: There are peculiar groups of fat-holding cells in the pulp. The smaller arteries and arterioles are hyaline.

Liver: The small sac described in the gross proves to be an aberrant gall-bladder.

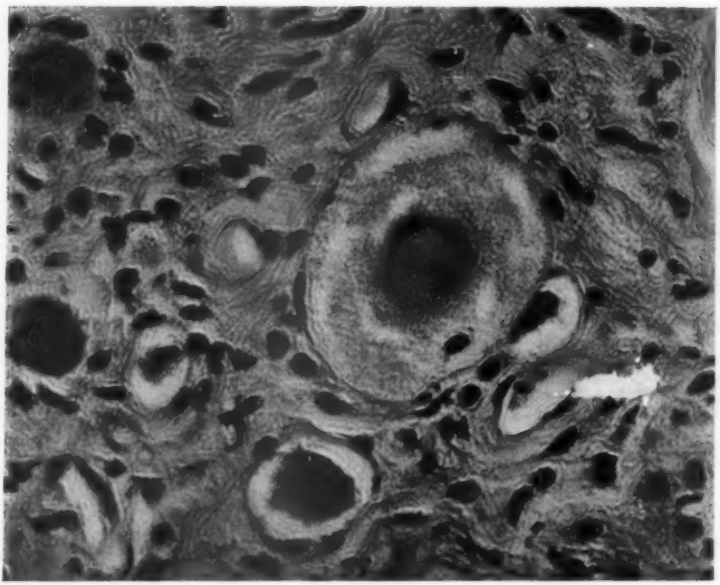

FIG. III. HIGH-POWER VIEW OF LARGE PALE GANGLION CELL
Finer structure lost. The cytoplasm throughout is coarsely granular

Adrenal: The zona fasciculata is a little broader than normal. There is no other change.

Thyroid: The fibrous stroma is increased. Many groups of acini are atrophic. In such places there are striking accumulations of lymphoid cells between the acini. In other places the acini are regular in size and outline and contain normal amounts of colloid. Voluntary muscle about the thyroid is normal.

Breast: The connective tissue is dense and hyaline. There is very little fat. The groups of acini are small and the acini themselves empty and shrunken.

Kidney: The epithelium is ragged and special stains show accumulations of fat and colloid droplets.

Oesophagus: Sections are taken from the upper, middle and lower portions of the oesophagus. In the upper the mucosa is mostly intact but there are some erosions. The submucosa is somewhat thickened and there are infiltrations of cells chiefly mononuclear but with a few polynuclear. In the middle the mucosa is

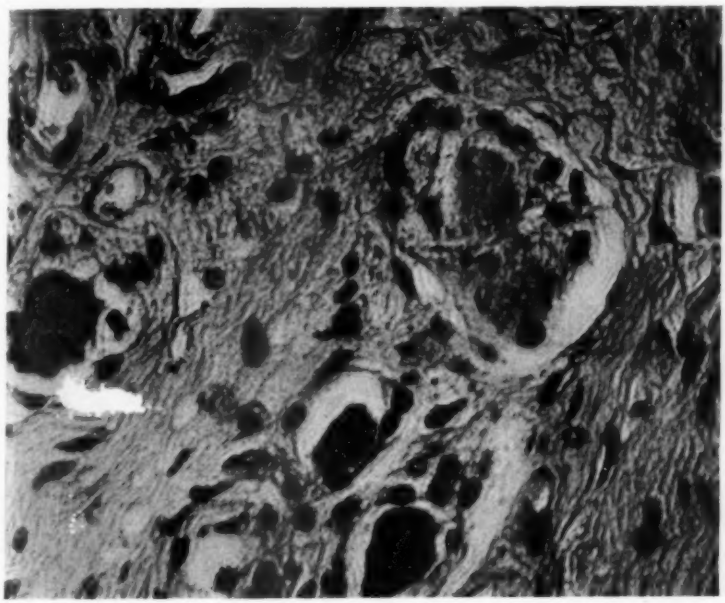

FIG. IV. HIGH-POWER VIEW OF TWO SWOLLEN GANGLION CELLS LYING SIDE BY SIDE

The commencing disintegration is seen clearly. There is hyperplasia of the capsular cells.

almost entirely lacking. The submucosa is very thick, scarred and extensively infiltrated with cells. The scarring extends into the intermuscular region. At the lower end the same change is seen. Throughout, Auerbach's intermuscular plexus is present and intact; its ganglion cells appear normal. The muscle is normal. There is no hypertrophy.

Stomach: There is some scarring and cell infiltration of the submucosa in the region of the cardia. Auerbach's plexus is normal.

Sigmoid: The mucosa and submucosa are normal. The muscle coats show no evident hypertrophy. The intermuscular plexus is normal, the ganglia and ganglion cells are plentiful.

Rectum: The appearances are the same as in the sigmoid.

Peripheral Vessels: The upper end of the brachial artery on either side shows very little beyond slight intimal proliferation. A section is examined from the

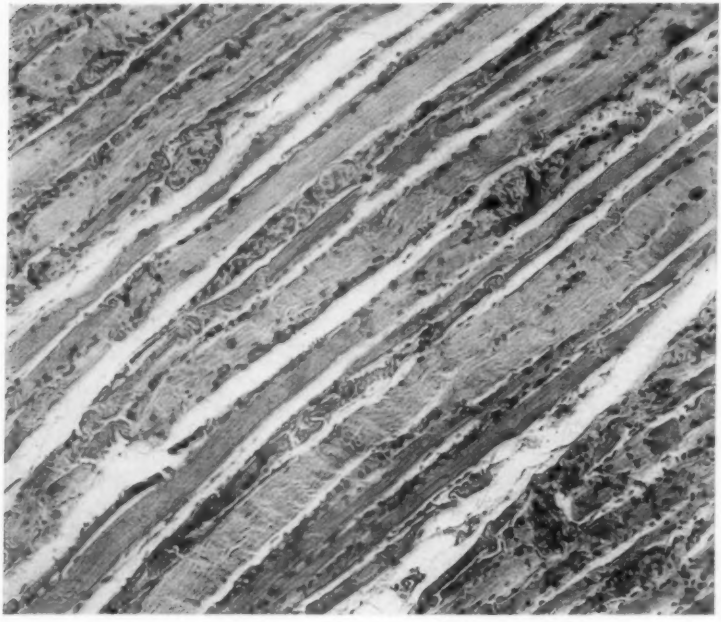

FIG. V. SECTION OF MUSCLE FROM THE THIGH

Small hyaline and dark-staining fibres alternate with large pale ones in which the separate fibrils are distinct. The sarcolemma nuclei of the former appear increased in number.

right radial at the wrist. There is very marked intimal thickening so that the lumen is greatly reduced. The other coats appear normal. Neighboring smaller arteries included in the section show a similar and more advanced change. The accompanying veins show a slight degree of intimal proliferation. Sections from the dorsales pedis arteries show again intimal proliferation but here so marked as to lead to a wellnigh complete obliteration.

Sections of the spinal cord and of peripheral nerves show nothing. The changes of greatest interest in this case are those found in the left lower cervical sympathetic ganglion. There seem to be fewer ganglion cells than normal. Many of those that remain show striking changes. Some are enlarged, pale, and show marked loss of finer structure; they appear "blown up" (Fig. III). There is a proliferation of cells forming the sheath to many of these nerve cells (Fig. IV). Others of the ganglion cells are small and shrunken. They stain deeply and contain excessive accumulations of brown lipochrome pigment granules. It is felt that the large pale disintegrating cells must present other than postmortem changes. Such changes have not been encountered in a series of controls examined of which some are taken into the fixative fluid at intervals after death longer than in this case. As to the shrunken deeply staining cells, it is believed that these are abnormal also but perhaps with less conviction. Lipochrome granules are frequently found in the peripheral sympathetic cells, indeed they may be said to be normal; a certain degree of shrinking of the ganglion cells is to be seen in normal controls but never to anything like the degree seen in the cells under consideration. The question must remain a matter for personal opinion. The blood vessels in the ganglion show slight intimal proliferation but without much encroachment on the lumen. Some have accumulations of lymphocytes in the adventitia. A stain for connective tissue shows the presence of fine strands throughout the ganglion but these are little in excess of the normal.

It is clear that we are dealing with a case of diffuse scleroderma. The clinical history and the gross appearance of the skin are sufficient to establish such an opinion, while the microscopical findings are characteristic. The atrophy of the papillae, the disappearance of hair follicles, sebaceous and sweat glands from the densely scarred dermis, the pigmentation of the rete Malpighii and even the accumulation of pigment in the upper layers of the dermis around small vessels (Gordon (1)) are all well known; even the hypertrophy of the musculi arrectores papillae is not unusual and has been described on several occasions since it was first noticed by Rossbach (2). The process of scarring often proceeds beyond the dermis into the subdermis as in this case, but the atrophy with disappearance of the adipose tissue is not a constant feature and, when present, depends probably rather on general inanition and cachexia than on any local change. Turnbull (3) ascribes the changes in the skin in a case examined by him to inflammation, a residuum of which he sees in a perivascular cell infiltration, and such an interpretation has been adopted by others. While in one area in this case, namely, in the skin from the chest, some degree of perivascular infiltration was noted, there was nothing else to suggest an

inflammatory process. It is true, however, that oedema of the skin is said to be characteristic of the early stages of scleroderma and has indeed been said by some authors to constitute the first stage of the disease. Moreover, at this time the areas may be tender and both of these facts suggest that possibly a subacute inflammation may be in progress. On the other hand, in a case of acute diffuse scleroderma examined by MacCallum (4) there were no signs of inflammation of any sort, although the patient had died four weeks after the first sign of illness during which the course had been febrile and the skin hot and tender.

The atrophic changes which are found in the voluntary muscles of the thigh are very striking. Jarisch (6) describes similar changes together with an overgrowth of interstitial tissue, presumably as a late result of the atrophy. He further points out that these changes are not secondary to the sclerosis of the skin since they may develop in a region over which the skin is normal. On the other hand, it is possible that they may result as part of the general cachexia together with disuse, even when the overlying skin itself is normal. As alternatives to this, the atrophy might result either as a direct result of the changes in the sympathetic system or as a sequel to diminished blood supply through narrowed arteries. The relation of the sympathetic nerves to the voluntary muscles has received much attention of late and probably the final word has not yet been said. Tower (20), however, has shown recently that no demonstrable changes appear in the voluntary muscles as a result of experimental section of the sympathetic nerves and this would argue against any relationship in the present case. As to the part played by the partial occlusion of the vessels and the consequent decrease in the blood supply in producing the atrophy, it may be pointed out that in the great majority of cases recorded in which the vessels in the altered muscles are mentioned some degree of occlusion is noted, which would suggest that there may well be some connection between the two.

Any examination of the literature concerning scleroderma reveals the confusion which exists between this condition and Raynaud's disease. In a large number of cases both diagnoses are made either contemporaneously or at different stages of the disease, and often it is impossible to be sure with which disease one is dealing. The history

of this patient is a case in point. As is usually the case, the symptoms and changes commence in a manner suggestive of a slightly atypical Raynaud's disease with circulatory changes in the extremities, especially the fingers. Subsequently, changes characteristic of scleroderma appear and often dominate the picture and the diagnosis, which originally has been one of Raynaud's disease, is changed to scleroderma. Kaufman (5) says that the form of scleroderma which is symmetrical and confined for the most part to the extremities,—sometimes called sclerodactylia—often begins *with symptoms of Raynaud's disease* and progresses with atrophy of the bones and mutilation of the fingers. The implication is apparent,—that one is not dealing with true Raynaud's disease but only with a certain phase of scleroderma in which the changes simulate that condition. So little is known about the pathology and pathogenesis of either condition that perhaps little can be done yet to clear the confusion, but it is hoped that some of the features of this case, especially the changes in the sympathetic cells to be discussed later, may help in this direction.

The changes in the vessels as found in this case are frequently but not invariably present, even when there has been nothing to suggest Raynaud's disease. Wolters (6) was the first to describe such changes in full and considered them as the essential and most important changes. On the other hand, they may be completely lacking in cases of pure scleroderma, although apparently almost always present when the case presents symptoms suggestive of vaso-motor disturbance. They resemble, of course, very closely the changes in the vessels which form an almost constant feature of Raynaud's disease. In this latter condition it is usually thought that the anatomical changes in the vessel are secondary to vaso-motor disturbances—spasm and the like—which in turn are due to some rather hypothetical nervous lesions. Whatever may be the truth of this surmise there is no doubt that such an endarteritis serves to connect certain cases of scleroderma with Raynaud's disease.

It seems certain that the lesions described in the sympathetic ganglion in this case are of utmost importance. In the past, lesions of different parts of the nervous system have been described in connection with scleroderma.

Herzog (7) found cysts in the course of certain of the dorsal nerve roots and in close connection with the dorsal root ganglia. Marburg (8) had already described similar cystic dilations in a series of cases, three of which showed extensive trophic disturbances of the skin. Westphal (9) found sclerotic areas in the brain; Calvet and Luys (10) sclerosis of the gray matter in the medulla and anterior horn of the cord. Schulz (11) described degeneration of anterior roots and nerve trunks while the central nervous system showed no changes. Harley (12) described a case in which the disease was limited to the upper limbs and in which autopsy showed the sympathetic chain on both sides from the lower cervical ganglion downwards to be embedded in densely thickened and scarred pleura. Jacquet and de St. Germain (13) described cavities in the gray matter, more especially in Clarke's column, at the lower end of the cervical enlargement. They quote, without giving references, Méry as having found scleroderma in connection with tabes, and Hallion in connection with infantile paralysis. Probably the connection is fortuitous. Steven (14) found in one case atrophy of the gray matter of the anterior horn.

On the other hand, detailed examination of the nervous system has often failed to show any changes. On the clinical side the connection of scleroderma with the nervous system is more apparent. The disease is associated frequently with the condition known as hemiatrophy and with conditions grouped under the heading of trophoneuroses. Moreover, the distribution of the lesions in the skin follows frequently the approximate distribution of nerves or nerve roots. If we are to believe that the condition is often, if not invariably, due to some lesion in the nervous system and perhaps more especially the sympathetic nervous system, then the connection with Raynaud's disease must become even more certain. The recent work of Adson (15) and others, which has shown that this latter condition can be relieved and in certain cases cured by sympathetic neurectomy, must surely go a long way towards confirming the opinion that the disease is due to definite changes in the sympathetic nervous system. Why some cases present symptoms predominately of Raynaud's syndrome while others show more evident changes of scleroderma it is impossible at the present time to say, but it seems probable that the reason for the confusion and the combination of the two diseases which exist must depend on the fact that both are due, in many cases at least, to the same pathological changes.

The abnormalities of the intestinal tract are of great interest and importance. It seems clear that both the oesophageal and the in-

testinal dilatations were secondary to conditions of spasm occurring at the cardiac and pelvi-rectal sphincters, although the absence of any demonstrable hypertrophy shows that the spasm was of slight degree or at least intermittent and not continued over a long period. It has been pointed out (16) in another place that spasm of these sphincters must be due to an irritative lesion of the sympathetic nervous system. If this lesion were progressive, it is obvious that the spasm should in the course of time be relieved by the very advance of the disease paralysing the sympathetic nerves. An examination of the clinical history in this case suggests that such was the event here. The oesophageal symptoms after the course of years began to improve, while the intestinal trouble which began so much later never reached such a stage of improvement.

Visceral disturbances of similar nature have often been described in connection with scleroderma (see Goodhart (17) and others) and appear to be a definite part of the disease.

Perhaps the most attention in the past has been paid to the endocrine glands in connection with this disease. This side of the question is critically and impartially reviewed by Castle (3). Disease of the thyroid occurs so often in association with scleroderma as to make it seem more than coincidence. There is, however, nothing uniform about the thyroid disease which is at times one of hyperfunction, at others of hypofunction. The adrenal shows, on occasion, lesions of one sort or another and the pigmentation which is such a feature of the disease draws attention to this gland. The only other gland of internal secretion which has received much attention is the pituitary, and here again diverse lesions have been noted on occasion. In the case under consideration the pituitary could not be examined, but the X-ray showed changes in the sella turcica which suggested that the gland must have been atrophic. The thyroid and adrenal showed slight changes which it is difficult to evaluate. Altogether the connection between the endocrine glands and scleroderma is vague and unsatisfactory. It has been suggested that whatever connection there is depends upon the action of these secretions on the sympathetic nervous system.

The occurrence of rheumatism in this case is of a certain interest. As long ago as 1880 Crocker (18) commented on "the frequent associa-

tion of scleroderma with acute rheumatism and peri- and endocarditis without other rheumatic symptoms." Many cases in the literature since then have shown this association, and in MacCallum's case (4) it was noted that "the earliest symptoms were rather those of acute rheumatic fever. This was confirmed at the autopsy." Klingman (19) in a recent paper describes a series of twelve cases of scleroderma, both acute and chronic, in eleven of which definite "rheumatic infection" either preceded or accompanied the skin changes. He believes that the "concomitant skin, muscle, nerve, bone and other trophic changes . . . . are the result of rheumatic lesions in many instances." As far as can be gathered from the case histories as published, four of his cases were certainly acute rheumatism or rheumatic fever and three possibly of this nature. The others give vague histories of muscle or joint pains at some time in the past. What connection can possibly exist between the two conditions it is difficult to imagine.

SUMMARY

A case of scleroderma associated with Raynaud's disease and dilatation of the oesophagus and colon is described. Lesions were present in the cervical sympathetic ganglion-cells, and the peripheral arteries showed an endarteritis. The relation of the anatomical findings to the clinical symptoms and signs is discussed and the present state of our knowledge on the subject reviewed.

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PERSISTENCE OF AN ACCELERATED RATE IN THE ISOLATED HEARTS AND ISOLATED AURICLES OF THYROTOXIC RABBITS: RESPONSE TO IODIDES, THYROXINE AND EPINEPHRINE[1]

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Animals, when treated with thyroid products over a sufficient period of time, exhibit an increased basal metabolic rate, tachycardia, loss of weight and elevated temperature. These changes are constant and are considered to be an expression of the effect of thyroxine on the animal organism. Attempts to reproduce these effects in acute experiments on animals, and on isolated tissues *in vitro* have been uniformly unsuccessful, due either to the great length of time required for the appearance of the specific thyroid effect or—in the case of isolated tissues—to the possibility that the specific effect may appear only through the agency of the intact organism.

These facts are responsible for the discrediting of a large amount of experimental work in which immediate but non-specific results have been obtained from thyroid products. The advent of crystalline thyroxine has demonstrated that most of these phenomena were due to proteins or other impurities in the material used.

During the course of the experiments reported below it was found that the hearts and auricles of thyroid-treated animals, when isolated, continued to beat at a much faster rate than similar preparations obtained from normal animals. This phenomenon was constant and did not tend to wear off during the course of the experiment.[4]

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[4] As a control, large doses of atropine were injected into normal animals subcutaneously. When acceleration of the heart rate occurred, the animals were killed and the auricles isolated at once in the Dale bath. The acceleration due to atropine was found to disappear within 20–30 minutes.

It seemed to indicate a persistence of the specific thyroid effect on the isolated tissue and was the basis for a comparison of certain pharmacologic reactions of the two types of hearts.

METHOD

Healthy rabbits were used in all experiments. They were kept in clean cages, fed on oats and cabbage and observed frequently. Weights were recorded upon obtaining the animals, before sacrificing them and several times in the interim. Electrocardiograms were taken every few days in order to follow changes in the heart rate. Some rabbits were fed thyroid gland (desiccated and powdered) in doses varying from .104 gm. to .390 gm. daily over periods varying from 2 to 81 days. Others received thyroxine (Roche) by intramuscular injection every second or third day in doses sufficient to average from .05 mg. to .15 mg. daily over periods varying from 6 to 25 days. Evidence of thyroid effect usually appeared at between 24 and 48 hours and became more marked the longer the animals were kept on the substance. Tachycardia, tachypnoea, rapid loss of weight and occasionally diarrhoea were observed. All animals were killed by a blow on the head, the chest quickly opened and the heart removed and placed at once in iced Ringer-Locke's solution. In some experiments the heart was left intact and was set up in the Lehendorff apparatus and perfused with oxygenated Ringer-Locke's solution adjusted to pH 7.4 at a temperature of 35°C; these are hereafter referred to as isolated hearts. In other experiments the auricles were dissected free under the iced saline solution and set up in a Dale bath of 100 cc. capacity, which could be quickly emptied and refilled with Ringer-Locke's solution adjusted to pH 7.4.[5] The bath and all the solutions to be used were immersed in a constant-temperature water-chamber kept at 35°C. Warmed oxygen was bubbled continuously through the solution in which the auricles were suspended. These preparations are hereafter referred to as isolated auricles.

The contractions of the preparations were recorded on a revolving smoked drum through light aluminium muscle levers. In the case of the isolated hearts a small hook was passed through the epicardium

[5] Bicarbonate buffer. The pH of the solution in the Dale bath soon rose to 8.0+ as oxygen was bubbled through.

near the tip of the ventricle and connected by a fine thread and a pulley to a spring lever. The isolated auricles were anchored by one tip and suspended by a fine thread directly from the other tip to a gravity lever. Spontaneous rhythm recommenced in every instance upon perfusion with or immersion in the warm Ringer-Locke's solution, and persisted until the experiment was terminated. Following adjustment to the desired amplitude, the preparation was allowed to settle down, a control tracing was taken and the conditions of the experiment were then altered by the addition of different drugs and solutions. Determinations of the pH of the fluid bathing or perfusing the preparation were made frequently. The time marker was set to mark at one second intervals. The coronary flow was measured directly by collecting the perfusate over known periods as it was discharged from the heart. In a few instances the isolated auricles of a normal and thyroxinized animal were set up in the same bath and made to record, one above the other, on the same smoked drum. This was thought to offer a better control than when the same procedures were carried out on the two preparations separately.

RESULTS

Effect of induced hyperthyroidism on the body-weight and the rate of isolated heart and isolated auricle

Table 1 indicates the total amount of thyroid material administered to each animal, the number of days during which it was given and the average daily dose. It will be observed that the amount of thyroid material administered and the duration of feeding bear little relationship to the weight loss and the rates of the isolated preparations. This is doubtless due to the varying susceptibility of the animals to the thyroid material. This fact has been frequently noted by other observers and there is no adequate explanation for it. Thus, in Experiment 39, the animal actually gained 14 per cent in weight, although fed relatively large doses of thyroid over 48 days, while in Experiment 43 there was a loss of 35 per cent in weight on a smaller dose fed over less time. Similarly, there is often no relationship between the degree of tachycardia exhibited by the isolated preparation and the loss of weight of the animal from which it has

been taken. No studies were made on the oxygen consumption of these animals, but it would be interesting to know if a parallelism exists between the rate of the isolated heart and the rate of oxygen

TABLE 1

Effect of thyroid-feeding and thyroxine administration on the body-weight and rate of isolated Heart and isolated auricle

EXPERIMENT NUMBER	DAYS ADMINISTRATION THYROID OR THYROXINE	TOTAL AMOUNT THYROID OR THYROXINE	AVERAGE AMOUNT PER DAY	LOSS OF WEIGHT		MAXIMUM RATE ISOLATED PREPARATION
				Grams	Per cent	
	*	Thyroid	Thyroid			Heart
		grams	*grams*			
39*	48	7.21	0.150	+142*	+14*	234
40	44	5.95	0.135	425	18	265
41	36	3.83	0.106	227	13	213
42	29	3.45	0.119	708	27	198
43	35	4.09	0.117	793	35	186
50	81	8.45	0.104	510	31	252
		Thyroxine	Thyroxine			Heart
		mg.	*mg.*			
51	18	1.40	0.078	748	40	168
52	20	1.65	0.082	509	34	210
53	25	1.25	0.050	85	9	192
54	6	0.90	0.150	0	0	168
55	†	1.20		737	43	198
56	12	1.70	0.140	147	7	165
		Thyroid	Thyroid			Auricle
		grams	*grams*			
18	21	3.31	0.158	538	27	201
19	30	4.09	0.136	708	33	177
20	2	0.78	0.390			189
21	2	0.78	0.390			171
22	34	5.75	0.169	312	16	198

* Gained in weight.

† After 0.8 mg. of thyroxine in 10 days the drug was withheld for 15 days because of great loss of weight and weakness. 0.4 mg. was given 48 hours before the experiment, resulting in a further loss in weight of 8.4 per cent.

use of the intact animal such as exists between the basal metabolic rate, pulse rate and cardiac output of patients with hyperthyroidism (13, 3, 6, 22).

Averages of the maximum rates (isolated heart or auricle) of preparations from normal, thyroid-fed and thyroxinized animals will be found in Table 2. They were registered early in each experiment after the preparation had settled down. The usual tendency to a gradual decrease in rate over a period of hours was seen in each instance. The rate of decrease in the thyroid-treated preparations and normal controls was approximately the same. It is obvious that the preparations from thyroid-treated animals beat at a much faster rate than those from normal animals. This was a constant and striking feature which persisted throughout each experiment.

TABLE 2

Average maximum rate per minute of the isolated hearts and isolated auricles of normal, thyroid-fed and thyroxinized animals

	NORMAL	THYROID-FED	PER CENT INCREASE	THYROXINIZED	PER CENT INCREASE
Isolated hearts.....	145 (16 exp.)*	224 (6 exp.)	54.4	183 (6 exp.)	26.2
Isolated auricles.....	125 (21 exp.)*	187 (5 exp.)	49.6		

* The maximum rates in individual experiments from which these averages are drawn are as follows:

Normal hearts: 174, 115, 159, 144, 108, 132, 138, 114, 192, 174, 160, 194, 141, 142, 148, 94.

Normal auricles: 126, 114, 129, 153, 105, 144, 111, 93, 150, 96, 126, 138, 150, 132, 120, 111, 96, 111, 150, 162, 114.

Effect of iodine and iodides. Table 3 illustrates the effect on the auricles from 10 normal and 3 thyroid-fed animals, of introducing sodium iodide, potassium iodide and iodine in varying concentrations into the bath. These concentrations in the bath were from 1:100,000 to 1:4,000,000, and, as can be seen in the table, were almost uniformly without effect on the rates. Further observations upon the effect of perfusion of 6 normal and 3 hearts from thyroid-fed animals with sodium iodide, in concentrations of 1:500,000 to 1:1,000,000 are shown in Table 4. In these experiments measurements were made of the rate and amplitude of contraction and coronary outflow. In 11 observations on normal hearts the rate decreased in 5 instances and showed no change in 6; the amplitude decreased in 8 and showed no change in 3; the coronary flow increased in 3, decreased in 2 and showed no change

in 6. In 3 observations on hearts from thyroid-fed animals the rate decreased in 1 and remained unaltered in 2; the amplitude showed no change in any of the three; the coronary flow decreased in 2 and remained unaltered in 1. The changes were not striking in any instance. The only significant result seemed to be a moderate

TABLE 3

Effect of iodine and iodides on the isolated auricles of normal and thyroid-fed rabbits

24 observations on 10 normal auricles

3 observations on 3 from thyroid-fed animals auricles

SUBSTANCE USED	DILUTION	NUMBER OF OBSERVATIONS	EFFECT ON RATE		
			Increased	Unchanged	Decreased
Normal auricles					
Potassium-iodide	1:4,000,000	2		2	
	1:2,000,000	3		3	
	1:1,000,000	5	2	3	
	1:500,000	1		1	
	1:250,000	1		1	
	1:100,000	1		1	
Sodium-iodide	1:2,000,000	2		1	1*
	1:1,000,000	3		2	1†
	1:200,000	1		1	
Iodine	1:2,000,000	2		2	
	1:1,000,000	3		2	1
Total.....		24	2	19	3
Auricles from thyroid-fed animals					
Sodium-iodide	1:1,000,000	3		2‡	1§

* Irregular rhythm.

† Irregular rhythm before iodide.

‡ Rate was unchanged after thyroxine 1:100,000.

§ Rhythm irregular. Rate had been decreased after thyroxine 1:100,000.

decrease in the rates of 5 of the 11 normal hearts and in amplitude of 8 of the 11. In view of the fact that the isolated auricles showed no such response to similar concentrations of sodium iodide, it might be supposed that a relationship existed between the coronary flow and the rate and amplitude of the hearts which appeared to be affected by the drug. No such relationship obtained. Furthermore, the

decrease in rate and amplitude were found more constantly with the lower than with the higher concentrations of sodium iodide.

These results are interesting in view of the recent work of Guggenheimer and Fisher (14) who obtained coronary dilatation with bromides and iodides in concentrations of 1:100,000 to 1:1,500,000. The effects were more marked in the higher dilutions until an optimum was reached. There was slight diminution in amplitude but little

TABLE 4

The effect of sodium iodide and thyroxine on the isolated hearts of normal and thyroid-fed rabbits

11 observations with sodium iodide on 6 normal hearts
8 observations with thyroxine on 5 normal hearts
3 observations with sodium iodide on 3 hearts from thyroid-fed animals
5 observations with thyroxine on 4 hearts from thyroid-fed animals

SUBSTANCE USED	DILUTION	NUMBER OF OBSERVATIONS	RATE			AMPLITUDE			CORONARY FLOW		
			Increased	Unchanged	Decreased	Increased	Unchanged	Decreased	Increased	Unchanged	Decreased
Normal hearts											
NaI	1:1,000,000	4		1	3			4	1	2	1
	1:750,000	5		4	1		3	2	1	3	1
	1:500,000	2		1	1			2	1	1	
Total.....		11		6	5		3	8	3	6	2
Thyroxine	1:400,000	8		5	3	2	4	2	3	3	2
Hearts from thyroid-fed animals											
NaI	1:750,000	3		2	1		3			1	2
Thyroxine	1:400,000	5	1	4		1	2	2	4		1

change in rate. Freund and König (12) were unable to confirm these findings. Macht (19), who made a careful study of the effect of iodides on isolated perfused hearts, found that the diminution of rate and amplitude seen when potassium iodide was added to the perfusate was largely due to the potassium ion. It is significant, therefore, in the experiments shown in Table 3, that of 13 observations on isolated auricles there was a change of rate upon the addition

of potassium iodide in only 2 cases—both of which showed an increase. Finally, it is to be noted that there was no difference between the behaviour of preparations from normal and hyperthyroid animals upon the addition of iodine and iodides.

Effect of thyroxine and desiodothyroxine. It was not expected that thyroxine and desiodothyroxine[6] when exhibited in acute experiments would produce any significant changes suggestive of a specific thyroid effect on the tissue. The findings of Oswald, von Cyon, Eiger, Asher and Flack, and others, on immediate tissue responses to thyroid products have been shown, one by one, to be due to non-specific substances incorporated in the material used.

Table 4 indicates the effect of perfusing hearts from normal and thyroid-fed animals with thyroxine 1:400,000 in the perfusate. It is obvious that no constant changes have occurred save in the case of the latter group, 4 out of 5 of which exhibited an increased coronary flow and 1 a decreased flow. These changes were not striking.

Table 5 shows the effect of thyroxine and desiodothyroxine in concentrations of 1:20,000 to 1:250,000 on auricles of normal and thyroid-fed animals. Of 21 observations the rate remained unchanged in 14 instances and decreased in 6. It may be said then that thyroxine and desiodothyroxine produced no significant change. This is in agreement with other observers who have used thyroxine on isolated tissues or in acute experiments on the intact organism (17, 4, 15, 18).

Effect of epinephrine. There are many points which suggest that the adrenals are closely connected with the phenomena of hyperthyroidism. No conclusive proof exists, however. Experimental evidence is based largely on the heightened response to epinephrine observed in the intact organism, or in isolated tissues when thyroid products are added with the epinephrine. Enhancement of the effect of epinephrine, obtained by many workers (2, 8, 9, 16, 20, 21, 5, 11) has since been shown to occur with histamine, tyramine, iodotyrosine, and numerous organ extracts (20) and cannot therefore be considered a specific thyroid effect. Furthermore, such results are not obtained when crystalline thyroxine is used (17, 10, 7, 18). Re-

[6] We are deeply indebted to Dr. C. R. Harington for our supply of desiodothyroxine.

markably few experiments have been made with epinephrine on isolated tissues removed from hyperthyroid animals. Reynolds (23) found no difference in the response of isolated strips of intestine from normal, athyroid and hyperthyroid rabbits when epinephrine was added to the bath. He felt that the epinephrine may have been decomposed by the Tyrode solution. Schermann (24) reports

TABLE 5

Effect of desiodothyroxine and thyroxine in acute experiments on the isolated auricles of normal and thyroid-fed rabbits

14 observations on 8 normal auricles
7 observations on 5 auricles from thyroid-fed animals

SUBSTANCE USED	DILUTION	NUMBER OF OBSERVATIONS	EFFECT ON RATE		
			Increased	Unchanged	Decreased
Normal auricles					
Desiodothyroxine (Harington)	1:250,000	1		1	
	1:100,000	2		2	
	1:50,000	2		2	
	1:33,000	4		3	1
	1:20,000	2			2
"Thyroxin" (LaRoche)	1:100,000	3		3	
Total		14		11	3
Auricles from thyroid-fed animals					
"Thyroxin" (LaRoche)	1:100,000	6		3	3*
"Thyroxin" (Squibbs)	1:25,000	1	1†		
Total		7	1†	3	3*

* Irregular in one observation.

† Irregular with abrupt changes in rate.

that the isolated hearts of thyroidectomized dogs are much less sensitive to epinephrine than the normal heart.

Table 6 gives a comparison of the increased rates and amplitudes of hearts from normal and thyroid treated animals following the addition of epinephrine 1:2,000,000. The increased amplitude is seen to be about equal in both series. In 3 of the latter series, however, an increase in rate of 10 per cent or more occurred—a degree of increase

seen in none of the normals. Moreover, in Table 7, which indicates the effect of epinephrine on isolated auricles, the preparations from thyroid-fed animals generally showed a greater acceleration than the normals—although one normal (No. 27) showed the greatest acceleration of all. More experiments would seem necessary in order to settle the question. Certainly there seemed to be no difference in sensitivity to high dilutions (1:100,000,000) of epinephrine, nor differences attributable to the sodium iodide and thyroxine when these substances were also present in the Ringer's solution (See Table 7). It is to be remembered, of course, that the acceleration or rate in the two types of preparations upon the addition of epi-

TABLE 6

Response to epinephrine of the isolated hearts of normal, thyroid-fed and thyroxine-treated rabbits

Amount of epinephrine 1.0 cc.—1:2,000,000

	NORMAL						THYROXINE TREATED						THYROID-FED
Experiment number....	47	57	58	59	60	61	51	52	53	54	55	56	50
Rate.....	0	0	†	*	*	†	0	*	0	‡	‡	‡	0
Amplitude.....	‡	0	†	‡	†	‡	†	*	†	‡	‡	‡	†

* Increase in rate of 5 per cent or less or in amplitude of 20 per cent or less.

† Increase in rate of 5–10 per cent or of 20–80 per cent in amplitude.

‡ Increase in rate of over 10 per cent or of over 80 per cent in amplitude.

nephrine, though similar in per cent increase, is considerably greater in the actual number of beats per minute in the preparations from hyperthyroid animals. Inasmuch as the original rates of these were more rapid than the normal—their absolute acceleration was considerably greater. It is difficult to say which is the proper mode of stating the case.

Furthermore, if the increased acceleration (in beats per minute) is considered to be significant, it must still be shown that this is due to a heightened sensitivity to epinephrine and not merely to the more rapid rate at which the preparations from thyroid-treated animals were beating at the time of the addition of epinephrine.

In *summary*, then, it may be said that epinephrine brought about

TABLE 7

The effect of epinephrine on the rate of isolated auricles of normal and thyroid-fed rabbits

20 and 21 received a single dose of thyroid extract, 0.78 gm., 48 hours before experiment

EXPERIMENT NUMBER	PER CENT INCREASE IN RATE					
	Ringer's solution		Ringer's solution containing throxine, 1–100,000		Ringer's solution containing sodium iodide, 1–1,000,000	
	Dilution of epinephrine					
	1:10,000,000	1:100,000,000	1:10,000,000	1:100,000,000	1:10,000,000	1:100,000,000
Normal auricles						
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
24	10	6			13	
25	3	0	44	0		
26	9	4				
	9	5	17	8		
			8*	4*		
27	49	8				
	56	0	6	0	27	16
Auricles from thyroid-fed animals						
18	9		11	0		
	16				16	4
19	3	7				
		13		35		
		41				
20	18	6				
	16	5	17	0		
	15	4				
21	15	0				
	29	0	13	0	11	0
	11	0				
22	18	3				
	15	6	23	7	30	23

* Desiodothyroxine, 1:25,000.

similar increases in rate and amplitude (*per cent*) in preparations from normal and thyroid-treated animals. The increase in rate (*beats per minute*) was greater in the latter group than in normal preparations. There was no difference between the two groups of preparations in sensitiveness to the higher dilutions of epinephrine.

CONCLUSIONS

1. The isolated hearts and auricles of thyroid-treated animals continued to beat at a much faster rate (26 to 54 per cent) than similar preparations from normal animals. This effect persisted throughout each experiment.

2. Iodine and iodides in concentrations of 1:100,000 to 1:4,000,000 had no significant effect on the isolated auricles but caused moderate decrease in rate in 5 of 11, and in amplitude in 8 of 11 isolated hearts. There was no difference in the response of normal preparations and those from thyrotoxic animals. No changes were observed in coronary flow.

3. Thyroxine and desiodothyroxine in acute experiments had no constant effect either on normal preparations or on those from thyroid-treated animals.

4. Preparations from thyroid-treated animals responded to epinephrine with increases in rate and amplitude (*per cent*) similar to those of the normals. Acceleration of rate (*beats per minute*) was greater in the former preparations than in the normals. There was no difference in sensitivity to high dilutions (1:100 mil.) of epinephrine.

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THE OUTGROWTH OF ENDOTHELIUM AND CAPILLARIES IN TISSUE CULTURE[1]

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Distinct and recognizable endothelial and capillary outgrowths were seen in about 35 per cent of some 2000 cultures of the skin and subcutaneous tissues of 7- and 8-day chick embryos, in a Locke-bouillon-dextrose medium, (85–15–0.5). These outgrowths were probably all derived from preexisting capillaries and blood vessels within the explants. (1) In some instances it was possible to trace the direct connection of the outgrowths with blood vessels in the thinner parts of the explants. (2) The endothelial and capillary outgrowths that were followed from day to day always began as small projections from the explants and gradually and slowly grew peripheralwards, forming various sorts of strands, plexuses and patches of solid endothelial strands and capillary tubes in varying proportions. (3) Motion pictures show in a clear manner the peripheralward migration of endothelium and of capillaries, and the plexus formation. (4) There was no indication at any place that any of the endothelial cells differentiated *in situ* from mesenchymal cells that had previously migrated out from the explants. (5) During the migration period the endothelial cells could be distinguished from the mesenchymal cells by a somewhat more refractive and denser-appearing cytoplasm, by a less reticular form of the cell, and above all by their most marked characteristic, namely, that of forming distinct strands and plexuses of either solid cords or capillaries, or mixtures of solid strands and capillaries. Where single cells, short or long strands, capillaries, or even parts of plexuses became separated from the explants or from the proximal plexuses or strands, there was often some indication as to where the separation had occurred.

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Motion pictures show that such separations take place by migration. In addition to the migration of endothelium from the explants there was an increase in the number of cells by mitotic division which was frequently encountered.

As might be expected, there was considerable divergence in the character of the outgrowths and the plexuses (figs. 1–12). The variations were probably due in part to the many differences in the orientation, the size and the relation of the enclosed blood vessels to the surface of the small explants which were usually a millimeter or less in diameter. The amount of injury, the size, the source and the orientation of the explants to the coverglass also varied and added other factors. The endothelium within the explant probably varied somewhat in detail, as there may have been growing tips, small capillaries and small blood vessels. Variations in the mesenchymal outgrowths which always preceded the endocapillary outgrowths may also have had some effect on the latter. Other factors such as the lack of blood pressure, of blood streaming, and of the general regulating influences as they exist in the growing embryo, were perhaps even more important.

Some of the endocapillary plexuses were similar to those in the embryo and often surprisingly extensive (fig. 1). Most of them, however, were irregular, with thick and thin strands of loose and close meshes (figs. 2, 3, 4, 6, 7, 8, 9, 10, 11). Some of the patches consisted of very close meshes of solid strands or capillaries and resembled in some respects hemangiomata (figs. 2, 3, 9, 10). In general the coarser strands and vessels were adjacent to the explants and the more delicate ones were at the periphery of the plexuses. The peripheral part of a capillary plexus frequently continued into a solid endothelial plexus (fig. 11). Occasionally quite large lakes of blood cells surrounded by endothelium and connected with capillaries were found some distance from the explants.

Plexus formations of the endocapillary outgrowths were formed by the anastomoses of lateral branches or by the main trunks themselves with lateral branches of the same trunk or of neighboring trunks from the same explant or nearby explants.

The solid strands varied from one to several cells in thickness (figs. 8, 10, 11) and occasionally small lumina without blood cells

and far removed from a capillary were seen in them (figs. 5, 6). I am not sure as to just how such small isolated lumina without blood cells were formed but several methods suggest themselves. (1) The first and the most probable one is that they were originally connected with some capillary lumen in the outgrowth and later were separated by the outward migration of the part of the strand containing them. (2) A second guess is that the fluid or plasma was secreted between closely applied endothelial cells (3). A third guess is that they were formed by some sort of a vacuolization within the cells.

Most of the capillaries contained degenerating or dead blood cells. The degenerating red blood cells gradually lost haemoglobin and their nuclei became very small and deeply staining (figs. 3, 4, 5, 6, 11). There was no indication of any new blood cell formation either from the endothelium or any other place. These red and white blood cells were all at one time within the blood vessels and capillaries of the explant and flowed out into the surrounding area. In some cases it could be seen that these blood cells were continuous with blood cells in a blood vessel within the explant.

The motion pictures show that as the capillaries with their enclosed blood cells migrated, some of them were pulled completely away from the more proximal portions; or the connecting parts were pulled out into solid endothelial strands. In this way capillary lumina of various sizes and lengths and containing from one to many cells were completely isolated from neighboring capillary lumina with which they had been originally connected (figs. 4, 5, 6). It thus seems

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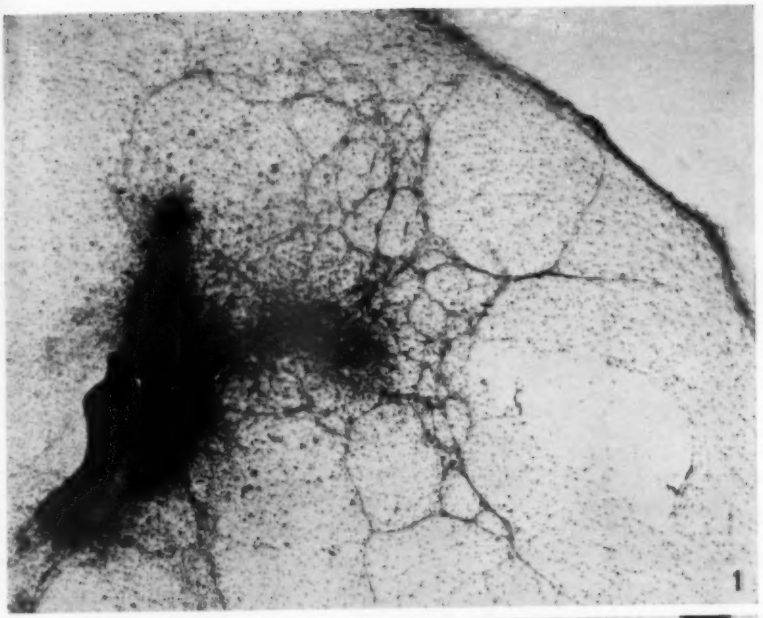
FIG. 1. (1146) Endocapillary plexus. 5-day culture, skin, 7-day chick embryo. Many of the strands are of solid endothelium. Some of the coarser ones have a lumen partly filled with granular debris and dead cells with small nuclei. This is more evident near the explant. At the periphery of the plexus the slender strands are often but a single row of much elongated cells with elongated nuclei. There are some disconnected endothelial cells more evident with the higher power. The reticular mesenchyme extends out beyond the plexus. There are many macrophages (small black dots) near the explant. × 50 dia. L-F, H and E.

L-F = 2 per cent formalin in Locke solution. Z-F = Zenker without acetic acid + 5 per cent formalin. H and E = haematoxylin and eosin stain.

FIG. 2. (1162) Endocapillary outgrowths and plexuses, 6-day culture, skin, 7-day chick embryo. (a) Isolated strands. × 50 dia. Z-F, H and E.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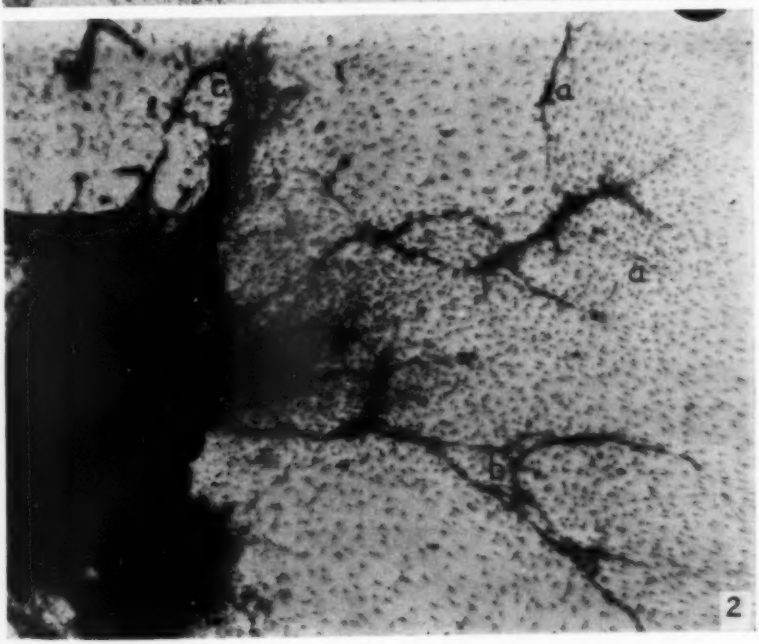
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quite certain that all the capillary lumina of the outgrowths containing blood cells were at one time continuous with those of the explants.

The endocapillary plexuses began to appear from one to five days after the cultures were made and persisted for varying lengths of time, sometimes for as long as the life of the culture which was usually not more than two weeks and frequently less. Many of the plexuses disappeared, however, before the cells of the cultures began to degenerate. Just what happened to the endothelial cells is not clear. They seemed to wander out among the mesenchyme cells from which they were not to be distinguished with certainty. This does not mean, however, that they became mesenchymal cells, and more extensive study may enable one to distinguish between them.

Aside from the mesenchyme cells about the only other type of cell which might be confused with the endocapillary outgrowths were, strange to say, the slender cells of skeletal muscle with one or two nuclei (fig. 12). Such cells frequently formed strands and plexuses somewhat like the endothelial ones. The muscle cells usually have a more deeply staining cytoplasm and nucleus.

The cultures contained many macrophages with varying amounts of ingested material. All those that were followed migrated from the explants and there was no indication of their arising from either the mesenchyme or endothelial cells of the outgrowth.

The fact that preformed capillaries can migrate in cultures makes one uncertain as to just how much of a capillary has (1) merely migrated out from the explant, or (2) been lengthened by the multiplication of cells in its walls (interstitial growth), or (3) been formed by the progressive extension of the lumen into the solid endothelial tip that increases parallel with this by the multiplication of the cells

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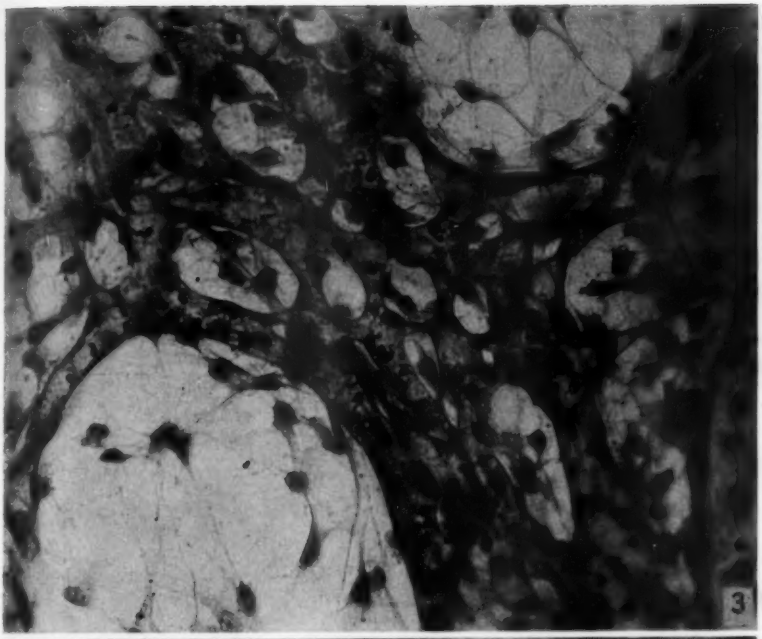
FIG. 3. (1162d) Part of plexus from location. (c), figure 2, showing close capillary plexus full of dead cells and granular debris. × 400 dia. Z-F, H and E.

FIG. 4. (1162b) Part of plexus from location (b), figure 2. Capillaries with dead blood cells and solid endothelial segments. × 400 dia. Z-F, H and E.

FIG. 5. (1157a). Short isolated Y-shaped capillary with dead blood cells and plasma. × 792 dia. Z-F, H and E.

FIG. 6. (1162c) Endocapillary strands, 6-day culture, skin, 7-day chick embryo. Amoeboid tips, small lumina with one or two dead cells and without cells. × 800 dia. Z-F, H and E.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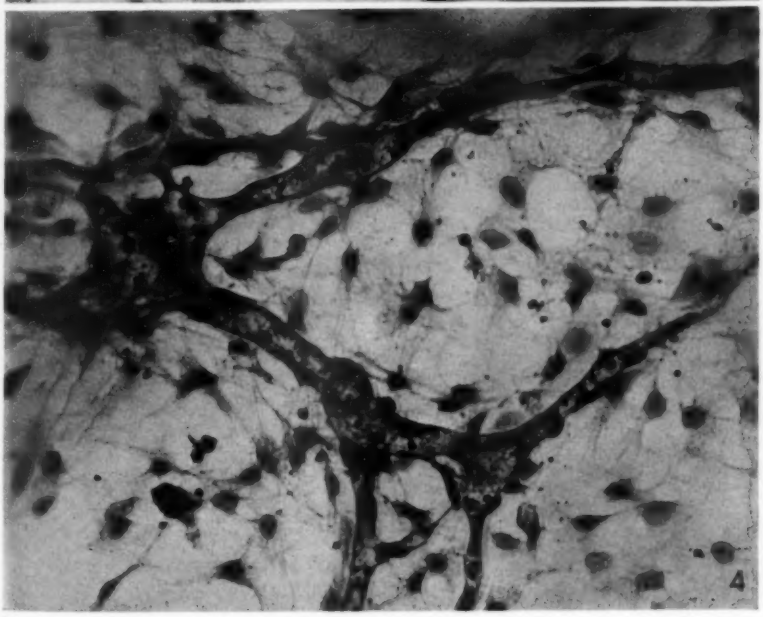
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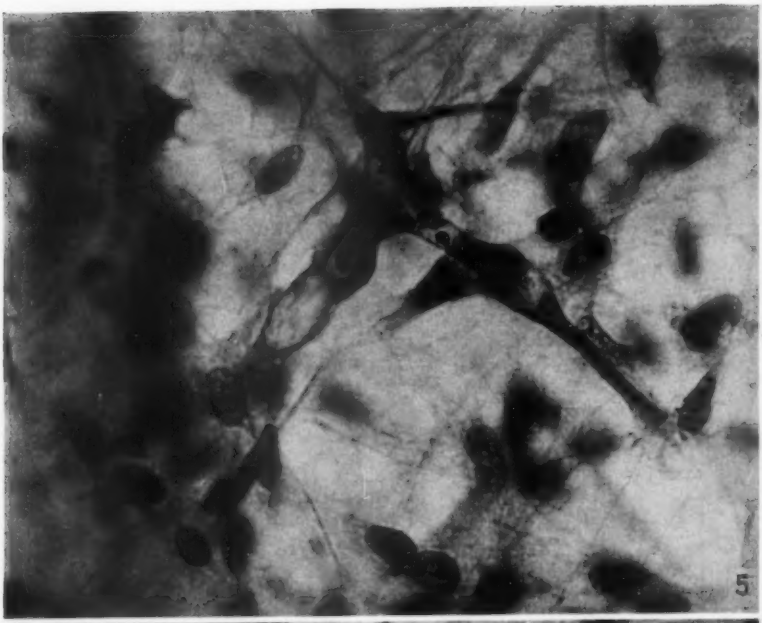
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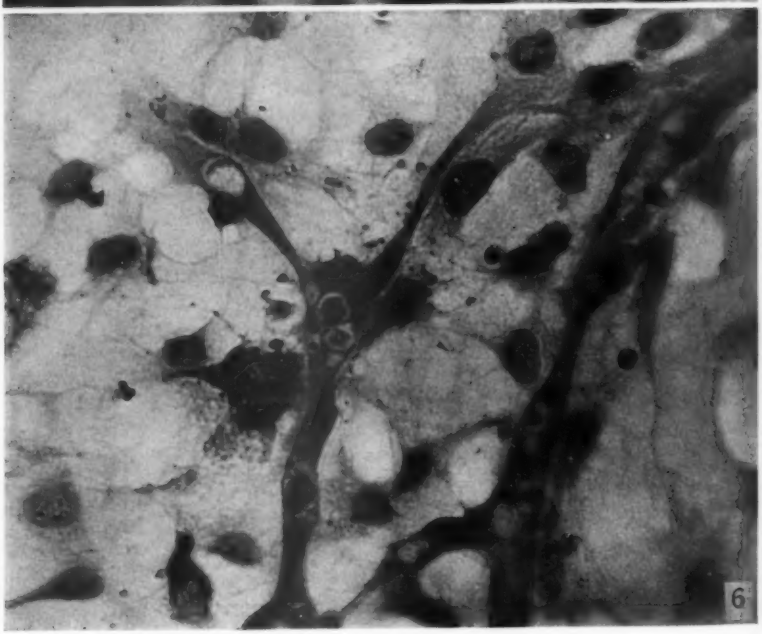
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there (apical growth). I am attempting to gain a clearer idea of these points by the use of motion pictures, since it is practically impossible to follow with the eye such complicated processes that are prolonged over hours.

There are two very surprising and outstanding features of the endocapillary outgrowths. The first is the plexus formation in the absence of any circulation or blood pressure. This would seem to indicate that the endothelium is already highly differentiated at this early stage, and just as ectoderm or endoderm form sheets, or kidney epithelium tubules, or mesenchyme reticulum, so endothelial cells due to something inherent in their structure and metabolism form plexuses of strands and capillaries.

The second outstanding feature of the outgrowths is the migration of preformed capillaries of various sizes with their contained blood cells. One would probably never have been quite sure of this without the evidence from the motion pictures. These pictures show capillaries with their contained blood cells and plasma moving outwards through the meshes of the mesenchyme. Just how this is accomplished is not quite clear, but it sometimes appears as though the capillaries were pulled along by solid amoeboid growing tips. In places the lumen may become obliterated by the stretching and then this solid endothelial segment may be pulled out thinner and thinner until finally the peripheral capillary part may become entirely separate and move off by itself.

FIG. 7. (1145d) Endocapillary plexus, 3-day culture, skin, 8-day chick embryo. Most of the strands are solid endothelium. (a) Isolated strands. × 50 dia. L-F, H and E.

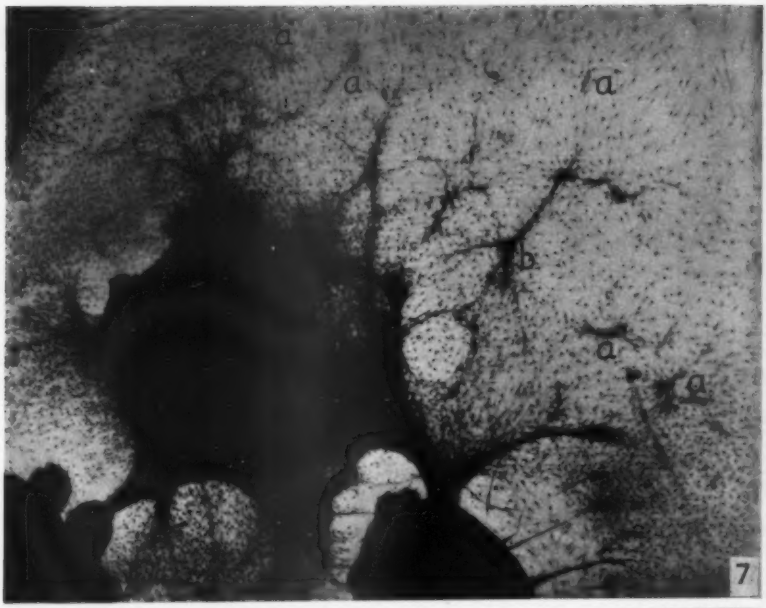
FIG. 8. (1145) Solid endothelial strands from location (b), figure 7. × 380 dia.

FIG. 9. (1161) Endocapillary patches, 6-day culture, skin, 7-day chick embryo. The strands and capillaries are closely packed. × 50 dia. Z-F, H and E.

FIG. 10. (1161a) Part of thick endothelial plexus at location. (a), figure 9. × 400 dia.

FIG. 11. (1160b) Endocapillary plexus, 6-day culture, skin, 7-day chick embryo. Capillary plexus is continued peripherally into endothelial plexus. × 400 dia. Z-F, H and E.

FIG. 12. (1164) Endothelium (e) and skeletal muscle cells (m), 3-day culture, skin, 7-day chick embryo. × 400 dia. Z-F, H and E.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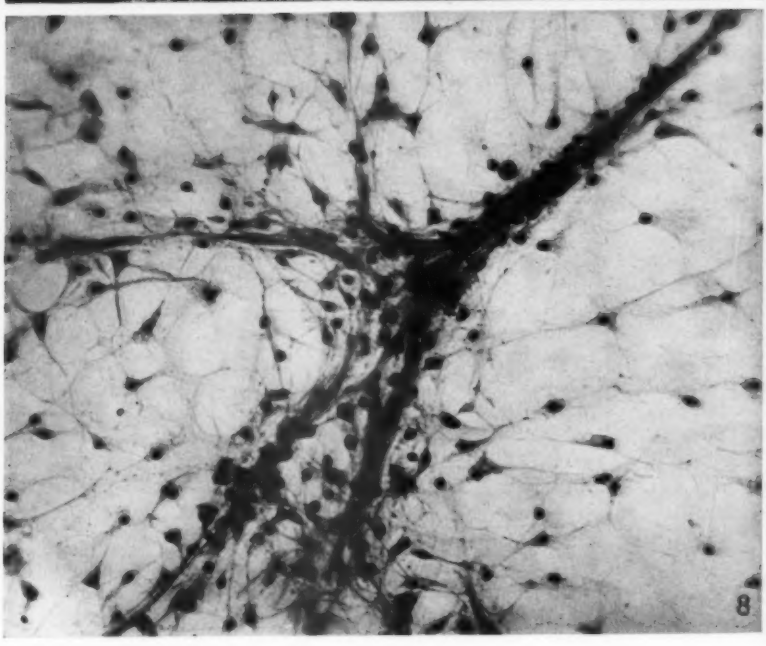
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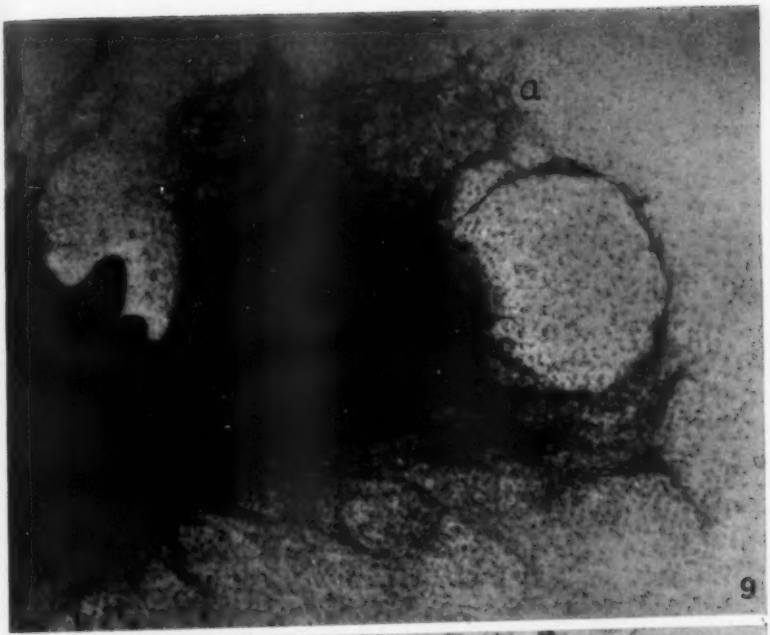
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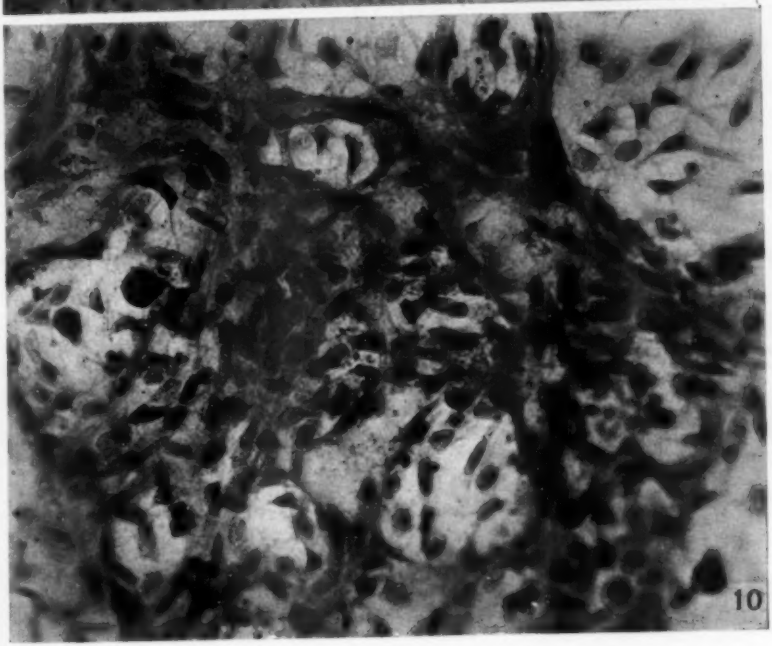
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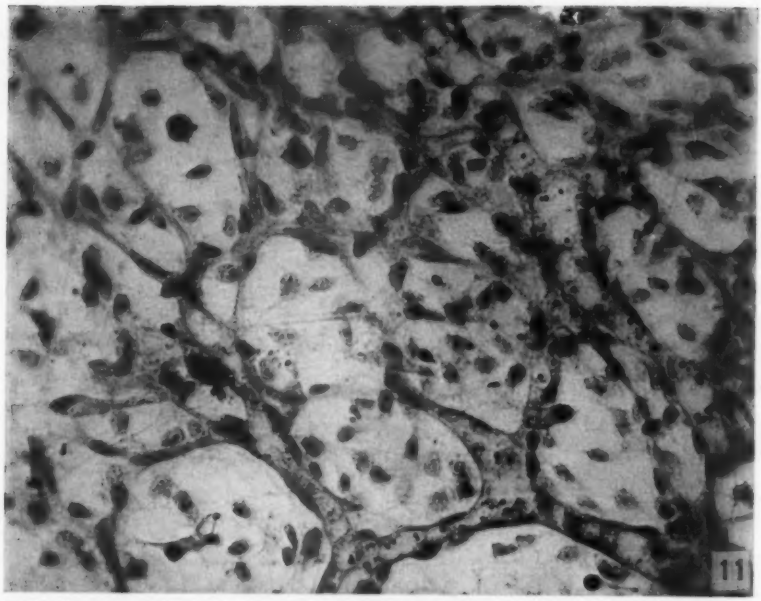
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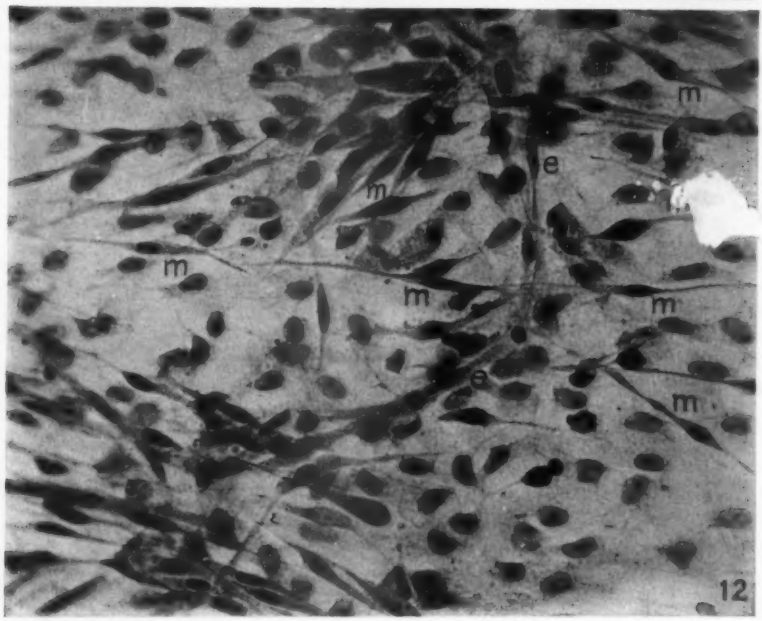
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These outgrowths are probably somewhat analogous to the spreading of capillaries during the development of the embryo and in wound healing. It is of course well known that endothelial sprouts migrate into healing wounds and non-vascular areas of the embryo and it may be that capillaries as such also grow out into such areas. As regards the spread of capillaries in the early developing embryo it is often taken for granted that, for a time at least, there is a differentiation of endothelium from the general mesenchyme, but the evidence for this is not good and it is quite possible that endothelium and mesenchyme are already differentiated from one another at the time they leave the primitive streak.

BOOK REVIEWS

Enzymes. (Monographs on Biochemistry.) By J. B. S. HALDANE. vi, 235. 8°. (*New York, Longmans, Green and Co., 1930.*)

This is an excellent short account of enzymes from the modern point of view and is particularly valuable from the theoretical side which has been comparatively neglected in books of this type. It is intermediate in type between Oppenheimer's encyclopedic "Die Fermente" and the usual general text-book. The authors and publishers are to be congratulated in having produced a new work rather than a revision of Bayliss's "Nature of Enzyme Action" which appeared in the same series; not only because, as the author states in his preface, the earlier book was a polemic for enzymes as catalysts, a view now almost universally accepted, but also because Bayliss in his preoccupation with adsorption neglected entirely the modern theories based on the law of mass action and put forward in 1913 by Van Slyke and Michaelis. The discussion of this theory is one of the best parts of the book. Using it as a basis, the kinetics of enzyme action, the effect of pH and the theory of specificity are discussed. The implications of experiments on poisoning of enzymes by metals, etc. occupy another chapter. Purification, molecular weights, and the problem of co-enzymes are dealt with and there is a section on the enzymatic processes concerned with biological oxidations. A feature of the book is the use of tables which condense a great deal of the information, allowing more space for discussion of its significance. The extensive bibliography attests the wide range of the author's reading. The book can be confidently recommended to all students of biochemistry and will be found necessary in any biochemical library.

G. S. E.

An Introduction to the Study of Physic. By WILLIAM HEBERDEN. Including a prefatory essay by LeRoy Crummer. 159 pp. $2.00. (*Paul B. Hoeber, Inc., New York, 1929.*)

The interest of this book is that it sets forth Heberden's ideas as to the preparation of young students for the Practice of Medicine. It confirms what is known of the clear insight, scientific attitude and general ability of the great clinician. While it applies, of course, mainly to the conditions of his time, there is much in it that meets the requirements of a modern Medical Education.

Heberden's "Some Account of A Disorder of the Breast" (Angina pectoris) is also included. Here, again, his known capacity for close observation and clear description is exemplified.

The Prefatory Essay by LeRoy Crummer describes the Original Manuscript of Heberden's "Introduction" here published for the first time, and gives an account

of him and of his background. As the editor observes about all biographies of Heberden, little is known of his life that is definite, and a good share of the prefatory Essay is taken up with the conditions of the period in which he worked. The book makes a very welcome addition to the few biographical references to Heberden now available.

M. H. F.

Diagnostic Methods and Interpretations in Internal Medicine. By SAMUEL A. LOEWENBERG, M.D., F.A.C.P. With 547 Illustrations, Some in Colors. 1032 pp. $10.00. (*F. A. Davis Company, Philadelphia, 1929.*)

The author has compiled a vast amount of material admirably arranged in outline. As stated in the preface, the purpose of the volume is to enable one to view human ills from the standpoint of the patient. Certainly the scope of this work in its extent gives one this opportunity, but herein the content loses much of its accessibility and the presentation in outline much of its force. In the effort to present the work from the viewpoint of the student as well as the general practitioner and the specialist, much material relating to methods of examination and normal findings is included. This is particularly true of the chapters dealing with the respiratory and the cardiovascular systems. While this is of course valuable to the student, it is too fragmentary really to serve his purpose and adds to the essentials of diagnostics in internal medicine much superfluous material. The chapter on the nervous system is well arranged and covers especially well the cardinal points of neurological diagnosis. The illustrations have been excellently selected and in all instances are good examples of the condition to be portrayed. The author has shown rare judgment in his selection. The reproduction is, however, poor, and by reason of this much of the value of the illustration has been sacrificed.

C. W. W.

A Practical Medical Dictionary. By THOMAS LATHROP STEDMAN, A.M., M.D. Eleventh, revised edition. Illustrated. 1222 pp. $7.50. (*William Wood and Company, New York, 1930.*)

As medicine advances new words will constantly appear, coined mainly from the Latin and Greek, sometimes from both, as is illustrated by the recent naming of the Pekin man, Sinanthropus. In the preface to the first edition of his dictionary, Dr. Stedman regards this custom of using mixed derivations as deplorable.

In this edition of the dictionary, all names of organisms proposed by the Committee on Nomenclature of the American Bacteriological Society have been incorporated. The newer terms used in physics and radiology and a number of new plates have also been added. Some of the illustrations should be brought up to date or discarded, *e.g.*, that of Commann's Binaural stethoscope and Janeway's sphygmomanometer which have only historic interest at the present time.

The contents of the appendix will be found especially useful; here can be found a concise table of drugs and doses, weights and measures, symbols, comparative

temperature scales, metric and English barometric scales, atomic weights of chemical elements adopted by the American Chemical Society in 1930 and a list of pathogenic microorganisms with their cultural characteristics.

C. L. G.

The Modern Dance of Death. By PEYTON ROUS. The Linacre Lecture, 1929. 51 pp. $1.00. (*Cambridge University Press, London, 1929.*)

"From the moment that the body becomes a going concern it must fight for its integrity. The Dance of Death begins long before birth, and never ceases throughout the lengthening period of what we call health." Are we winning over this Dance of Death, and what have been the contributions of medical science towards this fight, are the questions considered in the Linacre Lecture for 1929 by Dr. Rous. We do know that man's expectation of life has been increased since Linacre's time (1460–1524). What of the future? Have we reached the limit, or does modern medical science afford expectations that the span of life may be lengthened?

The outlook given by Dr. Rous is a gloomy one. In order to lengthen life, an entirely new type of reaction of the body to the causative agents of death is needed, so that the body will be able to cope with disease more effectively than it does at present. This change can not be discovered to be taking place in the body as a result of advances in our knowledge of disease. What has changed has been the clinical aspects of disease. The introduction of insulin and liver extract has not modified the body's reaction to diabetes or pernicious anemia; they have only altered the course of the disease.

Surgery also offers no hope. "The tendency on the part of the organism to play its game along the accustomed lines is so strong that the most radical of operative procedures seldom diverts it enduringly from its course." The author of the book shows how stagnant have been the attempts to improve the body by removal of organs. "Now surgeons have come reluctantly to realize that nearly all that the body possesses it has an earnest, if undisclosed, need for."

Substitutions of organs by drugs, by mechanical measures, by transplantation, are highly artificial devices which can never replace the multiplex function of living cells. Transplantation would be ideal theoretically, but practically it has failed. The following quotation from the book is delightful. "There was a time not far back when laboratory workers, having to recognize a perhaps exaggerated individuality in themselves and their fellows, could yet perceive but slight traces thereof in the smaller laboratory animals, least of all in the inbred albinos. One healthy white rat or rabbit seemed, so far as concerned visible responses, much the same as another, perhaps a little fatter, or thinner, older or sturdier, but that was all. Now we recognize what may be termed physical personalities in these creatures, personalities which, extending even to hardy tissues like the skin, involve these in disaster after transplantation." As physicists now recognize individuality in an electron, it is not surprising that so highly complex an organization as a red cell would have individuality, and individuality can not be conquered by external means.

The causes of death have changed during the past fifty years. "But there is a drab implication in the change, since in it one sees humanity marching up close to the ultimate barrier of age." Even if cancer, pneumonia, heart disease and nephritis could be checked, there is still the problem of old age, where involution of tissues begin. "The individuals who are now conserved throughout adult life die of diseases that have waited upon age from time immemorial but that have had few targets in the past, not hosts of them as now."

The only hope that Dr. Rous gives is that, in the future, mutations may occur which will enable the body to react to disease in a different and better manner than at present. He does suggest that more emphasis will be placed in the future on conservation of organs. A child will be told to tread cautiously in his youth in order to save his heart and kidneys for an old age, as now he is instructed to use a toothbrush to save his teeth.

There may be other ways of combating the Dance of Death, unknown today. It has generally been true that when men begin to regard a subject as closed, it opens out again. Johannes Müller claimed that the velocity of the nervous impulse was so rapid that it would never be measured; yet only a few years later Helmholtz did measure the speed with precision. Thus, new methods may be developed for combating the Dance of Death of which we have no knowledge at the present time.

The book is attractively bound, printed on excellent paper and has a copy of Hollar's engraving of Holbein's painting of The Physician on the cover. Written in lecture style, it makes entertaining reading, although some sentences are unnecessarily complex, as may be seen from the quotations given above. The historical contrast of the Dance of Death of Holbein with the modern Dance of Death is especially interesting.

C. L. G.

Medical and Surgical Reports of the Episcopal Hospital. Vol. VI. vii, 460 pp. 8°. (*Philadelphia, Wm. J. Dorman, 1930.*)

The sixth volume of the Episcopal Hospital (Philadelphia) Reports commemorates the seventy-fifth year of the hospital's existence. It contains forty-three separate articles, a large number of which have been published elsewhere; a few, especially those of an historical nature, contrasting the early days of the hospital with the present, have been written especially for this volume.

No attempt will be made to review here separate articles that cover a broad range of medical and surgical subjects.

C. L. G.

The Candiru the Only Vertebrate Parasite of Man. By EUGENE WILLIS GUDGER, Ph.D. With a Foreword by Aldred Scott Warthin. 116 pp. $1.50. (*Paul B. Hoeber, Inc., New York, 1930.*)

In this interesting little volume Dr. Gudger attempts to set forth the evidence at present available pertaining to human parasitism by the small South American

catfish, the Candiru. This animal, attracted by the odor of urine is said to enter the urethral and vaginal openings of bathers in the South American rivers. Rumors are many and authentic reports few on the subject. These latter Dr. Gudger has collected and here presented as evidence for the existence of the only known vertebrate parasite of man.

S. J. W.

Text-Book of Embryology. By FREDERICK RANOLPH BAILEY, A.M., M.D., and ADAM MARION MILLER, A.M. Fifth revised edition. 687 pp. $7.00. (*William Wood and Company, New York, 1929.*)

Another edition of this worthy text-book, in which the chapters on germ cells and the chapter on the nervous system have been considerably revised. Some of the older cuts begin to show the effects of twenty-years' service, *e.g.*, figs. 7 and 98.

G. L. S.

An Introduction to Vertebrate Embryology. By H. L. WIEMAN. First edition. 411 pp. $4.00. (*McGraw Hill Book Company, Inc., New York, 1930.*)

Throughout the American colleges and state universities a rather standardized premedical course has been developed, which is followed annually by a large number of students in preparation for meeting the entrance requirements of medical schools. Vertebrate embryology is naturally one of the subjects included in these courses and consequently an active demand has arisen for embryological textbooks of suitable scope and character. This need has been increasingly recognized both by the alert publisher and by the teacher who is called upon to conduct the course. Through the joint response of the two there have appeared in the last few years a number of embryological books of that type. The above "Introduction to Vertebrate Embryology" is the most recent offering. The McGraw-Hill Book Company was fortunate in securing so experienced an embryologist and teacher as Professor Wieman to assume the responsibilities of authorship. From his close contact with problems of general embryology, one can understand why the author has treated the cytological chapters at some length and why it so well constitutes an introduction to embryology. It is more than this, however, for in a brief way it outlines the story of organogenesis in Amphioxus, frog, chick, pig and man. One might wish parts of it treated more fully and provided with subsidiary details to which subsequent reference could be made as the need arises. Especially in the case of the medical student, it is apt not only to be his introduction into vertebrate embryology but also his sole acquaintance with the subject.

G. L. S.

Some Aspects of the Cancer Problem. By W. BLAIR BELL. 543 pp. $20. (*William Wood and Company, New York, 1930.*)

Under the editorship of its distinguished leader, W. Blair Bell, the important papers of the Liverpool Medical Research Organization are gathered herewith under a single cover. Since 1904, over sixty articles have appeared from this

group, covering widely diverse aspects of the cancer problem, including fundamental contributions to physiology, chemistry and pharmacology, as well as detailed studies on lead therapy. For example, Warburg's altered position, that a high glycolytic metabolism is not peculiar to malignant tissue, was independently arrived at by Bell and his co-workers. To present these researches in a unified whole, selected papers and addresses have been re-edited and placed in their logical rather than chronological sequence. An introduction and a running commentary by the editor have woven these discrete contributions into a readable history of the evolution of an hypothesis and its corollaries. There is a bibliography of 665 references.

The results of lead therapy are given in detail. Of 566 patients during an eight-year period up to November 9th, 1928, 360 died before treatment could be completed; but in 12 the disease was completely arrested and in 53 cases the patient was clinically cured. Many of the cured cases were inoperable and beyond hope from radiation. Whatever be the recurrences after lead therapy, the palliative results of this treatment alone, in the clinic at Liverpool, prove lead to be a valuable ally of surgery and radiation.

Regardless of the verdict of the next decade on lead therapy, this work is a brilliant example of scientific research and a revelation of the possibilities of group investigation.

R. F. C. K.

Einführung in die Medizin. Von Dr. Med. Henry E. Sigerist. 405 S. Rm. 14. (*Georg Thieme, Leipzig, 1931.*)

Within our present medical curriculum, medical education is very discontinuous. During the first three years of medicine, the student is confronted with many different subjects, each requiring a different technique and a different mode of thought. Given an individual subject, there is not much correlation with its historic past or its application to future studies. A few medical schools are giving introductions to surgery and medicine for first and second year students, but that does not help first year men as they start their work.

To bridge the gaps between past, present and future, Sigerist publishes an introduction to medicine for beginners and cultivated people. Written in a remarkably clear style, this book discusses the significance of anatomy, physiology, pathology and clinical subjects, showing how each subject fits into the general scheme of medical education and answering the frequently repeated question of the student, "Why should I study this subject?"

Professor Sigerist devotes his first chapter to the study of the structure of man. In a short time, the student obtains anatomical knowledge concerning man's body which has required hundreds of years of work and many workers to arrive at its present status. Primitive man, the Greeks, the surgeons and painters of the middle ages, Vesalius and his followers, the men who developed microscopy, all have contributed to our knowledge of anatomy, which is the basis of medical knowledge.

The development of physiology is illustrated by two examples, those of the circulation and of respiration. The story of Harvey's discovery of the circulation of the blood is well described. Harvey was an anatomist but he gave to anatomy a new aspect,—"*anatomia animata*," a study of movement, of dynamics, rather than of inert structure. With this newer anatomy, exact measurements were introduced into medicine. The rise of chemistry and physics was also reflected in medicine. This is illustrated by an historical account of the development of respiration. Professor Sigerist makes it very clear that the study of physiology is not as simple as the study of inorganic chemistry or physics, since physiology has another factor involved—life. "We can accurately determine the rhythm of the heart and the energy that is developed. But the fact that the heart does beat and the muscle contracts cannot be explained mechanically." Physiology forms the bridge between anatomy and the clinic. As anatomy is the study of a dead object, so physiology is the study of a living one, thus "the method of physiology is the method of the clinic."

But man is more than form and function. There is a third quality, "mind," that does not lend itself to anatomical or physiological explanation. Professor Sigerist makes a plea for the introduction of more psychology, philosophy and sociology into the premedical and medical curriculum. "The doctor deals continually with the intact man, with the totality of his human relationships." Sickness involves more than the individual, it is a problem of society. "Doctor and priest were one and the same in the primitive society." But today the doctor has taken over many of the former duties of the priest, which necessitates a very broad knowledge of man.

The next sections of the book are devoted to the study of disease. The historical development of the concept of disease is particularly good. It begins with primitive man, who thought that demons brought on sickness, and comes down to our present day concept of disease based on pathology. The course of the disease and the causative factors are discussed in the same clear manner as in the earlier chapters.

The rôle of the doctor in combating disease occupies the next section. This is divided into three parts, diagnosis, cure and prophylaxis. The last section of the book is devoted to the doctor himself. The antiquity of the profession, the relationship of the doctor to society throughout history constitute its main topics.

This book is unique in that it sums up the whole structure of medicine, which is based on many factors. Each factor is given recognition and the result is a coordinated picture which every medical student should have in his mind, but this generally does not obtain until after three or four years' study. Faber's "Nosography in Modern Internal Medicine" does give a similar picture but in a limited field and was not written primarily for the beginning student. It is to be hoped that a good translation will soon be forthcoming to make Professor Sigerist's book more accessible to English readers, for it should be read by every first year medical student along with Osler's "The Student Life."

C. L. G.